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PARALYSIS OF NERVE INDUCED BY DIRECT PRESSURE AND BY TOURNIQUET

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Although in clinical neurology peripheral nerve palsies induced by a tourniquet are uncommon, such palsies due to direct pressure of other kinds are frequently met with. Despite this, attempts to define the factors involved in the production of such lesions have been remarkably few. Lewis, Pickering and Rothschild [1] studied the paralysis produced by the application of pressure to human limbs both by the sphygmomanometer cuff and by localized pressure on single nerves. They elicited facts of great interest. The paralysis produced by a cuff had centripetal onset and affected touch before pain and pain before motion. The latency of onset with a cuff around the upper part of the arm was almost constant (paralysis at about the twenty-fifth minute) and was the same with pressures of from 150 to 300 mm. The cuff was without effect at pressures below the systolic blood pressure. When paralysis had commenced, the placement of a second cuff below the first, with the same pressure, and then removal of the first cuff were followed by recovery from the paralysis and its reassertion after a further latency. These authors concluded therefore that such paralysis was due to ischemia of the compressed segment, and not to peripheral stasis. It was found also, however, that the nerve immediately below the cuff became less excitable than the portion farther below. They expressed the opinion that pressure influenced conduction only by means of local ischemia. The centripetal progress and selective character of the paralysis were explained by greater sensitivity of larger nerve fibers to anoxia.

Pressure confined to the ulnar nerve at the elbow, or to the peroneal nerve where it crosses the fibula, induced a paralysis and anesthesia of slower onset than those in cuff experiments, the effects appearing concurrently in all parts supplied by the nerve and sparing pain sensation. Recovery was also more rapid on release of pressure than occurred in experiments with cuffs. These differences are difficult to reconcile. Lewis, Pickering and Rothschild [1] explained them on the basis of less accumulation of metabolites in conditions of localized pressure than with the more complete occlusion of vessels by a long sphygmomanometer cuff. The late involvement of pain sense from direct pressure on human nerves had earlier

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1. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb, Including Notes on a Form of Tingling, Heart **16**:1-32, 1931.

been noted by Bastien and Vulpian [2] and by Waller.[3] The last investigator observed that after compression of his own ulnar nerve for forty-five minutes recovery of motion and sensibility was complete only after eleven days.

These observations suggest that tourniquet paralysis is also the result of localized ischemia of the nerve at the level of the constriction, similar to that produced by a cuff. Lesions produced by the tourniquet, however, show certain clinical points of close resemblance to lesions induced by localized pressure on nerves, such as the radial or the peroneal, and certain points of dissimilarity to the paralysis produced by the pneumatic cuff by Lewis and associates.[1] The duration of pressure required to cause paralysis appears to be highly variable. Thus, patients will occasionally report a radial palsy after leaning the upper part of the arm on a hard object for as short a time as twenty minutes. Their estimate may have been faulty, but Waller, as previously noted, found persistent paralysis to result from forty-five minutes of pressure on the ulnar nerve above the elbow. Occasionally tourniquet paralysis will be produced after an application for some forty minutes, while at other times a tourniquet is used for an hour or more without damage. Some authorities (Auchincloss [4]) have advised use of a broad cuff instead of a narrow tourniquet, claiming that the latter is more likely to cause damage to the nerve.

Further, the paralysis is, in its milder degrees, often purely motor and is not associated with reaction of degeneration; the observation of a case of this type by one of us (D. D.-B.) excited our interest in this condition.

A young man had had a surgical operation on the forefinger for an old contracture following sepsis of the flexor tendon sheath. A tourniquet had been applied to the upper part of the arm for forty minutes. Sensation was impaired for twenty-four hours, and complete motor paralysis below the elbow lasted ten days, after which some power of flexion of the fingers and wrist appeared. Complete restoration of motor function occurred in about seven weeks. When he was seen four weeks after the onset, there was still no power of dorsiflexion of the wrist or fingers, and severe weakness of all the intrinsic muscles of the hand was present, though all these muscles showed normal electrical reactions and were only slightly wasted. The error of an earlier diagnosis of hysteria was apparent in the failure of the brachioradialis muscle to participate in flexion of the elbow.

This type of paralysis was evidently recognized in 1876 as due to localized pressure by Erb,[5] who said (page 393):

Even a slight mechanical action may so change the molecular constitution of the motor nerves as to abolish their power of conduction. . . . Experience teaches that motor nerves offer less resistance to such lesions than the sensory ones do.

In another place (page 424) the same author stated:

In many paralyses scarcely any alteration of electrical excitability is observed. . . . This is the rule . . . in slight traumatic paralyses as in paralysis of the radial nerve from pressure.

Later (page 551) he said:

In the slighter forms of musculospiral paralysis arising from pressure . . . the electrical excitability is usually quite normal, and it may often in such cases be satisfactorily employed

2. Bastien, J.-B., and Vulpian, A.: Mémoire sur les effets de la compression des nerfs, Gaz. méd. de Paris **10**:794-795, 1855.

3. Waller, A.: On the Sensory, Motory, and Vasomotory Symptoms, Resulting from Refrigeration and Compression of the Ulnar and Other Nerves in Man, Proc. Roy. Soc., London **12**:89-102, 1862-1863.

4. Auchincloss, H.: Surgery of the Hand, in Nelson Loose Leaf Surgery, New York, Thos. Nelson & Sons, 1941, vol. 3, p. 509.

5. Erb, W. H.: Diseases of the Peripheral Cerebrospinal Nerves, in von Ziemssen, H. W.: Cyclopaedia of the Practice of Medicine, New York, William Wood & Company, 1876, vol. 11.

to determine the position of the cause of paralysis in the nerve since below the point of lesion the excitability is normal, whilst no reaction can be obtained when the current is applied above it. . . . In one case of pressure paralysis (of the musculospiral nerve) I found the previously mentioned intermediate form of reaction of degeneration.

Lüderitz [6] compressed the sciatic nerve of rabbits, with the surrounding muscle, by means of a rubber band and observed that conduction of motor impulses was abolished before conduction of sensory impulses.

Dejerine and Bernheim [7] spoke of this loss of motor conductivity with preservation of electrical excitability below the level of compression and cited a case of radial nerve palsy from pressure during sleep, with autopsy twenty-five days later. They found wallerian degeneration only in the nerve to the supinator longus muscle. Close examination of the radial nerve in the upper portion of the arm and the other branches to the forearm revealed only a granular (*grénu*) appearance of the myelin sheaths throughout these nerves, with vascular congestion at the supposed point of pressure.

Nerve injuries with dissociated effects were frequent during World War I when a bullet or a shell fragment had passed close to a nerve without actually lacerating it or tearing its sheath. Thus, of 500 cases of nerve injury, Frazier and Silbert [8] stated that as a result of compression there were complete motor paralysis in 45 per cent, complete sensory loss in 15 per cent and complete reaction of degeneration in none. The phenomenon of electrical response limited to the nerve trunk below the lesion was noted eight months after suture of the radial nerve by Platt [9] and was followed by recovery of voluntary power some months later. Perthes [10] also noted this phenomenon after war injuries and cited it as an instance of true autogenous peripheral regeneration.

A British Committee on Nerve Injuries [11] stated (page 54) that with such partial or transient damage to the nerve "the axis cylinders are damaged but Wallerian degeneration does not take place; they temporarily lose their normal conductivity but retain trophic power over the distal segment of the nerve," and, later, that "in a simple case the function of the nerve is restored within a few days or weeks." We have not found any more detailed description or illustration of this interesting lesion, although Hassin [12] made reference to the paper of von Büngner,[13] in which it is stated that just proximal to ligature of a nerve some myelinated fibers may show thinning of the myelin sheath for a segment with a full sheath both proximally and distally. Ramón y Cajal [14] described and illustrated thinning of

6. Lüderitz, C.: Versuche über die Einwirkung des Druckes auf die motorischen und sensiblen Nerven, Ztschr. f. klin. Med. **2**:97-120, 1881.

7. Dejerine, J. J., and Bernheim: Sur un cas de paralyse radiale par compression, suivi d'autopsie, Rev. neurol. **7**:785-788, 1899.

8. Frazier, C. H., and Silbert, S.: Observations in Five Hundred Cases of Injuries of the Peripheral Nerves at U. S. A. General Hospital, No. 11, Surg., Gynec. & Obst. **30**:50-65, 1920.

9. Platt, H.: The Surgery of the Peripheral Nerve Injuries of Warfare, Bristol, John Wright & Sons, Ltd., 1921.

10. Perthes, G.: Beobachtungen bei elektrischer Reizung freigelegten verletzter Nerven im vergleich mit der neurologischen und histologischen Befunde, Deutsche med. Wchnschr. **45**: 897-900, 1919; Ueber das elektrische Verhalten von Muskeln nach Durchtrennung des zugehörigen Nerven, München. med. Wchnschr. **66**:1016-1017, 1919.

11. The Diagnosis and Treatment of Peripheral Nerve Injuries, Medical Research Council, Special Report Series, no. 54, London, His Majesty's Stationery Office, 1920.

12. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940.

13. von Büngner, O.: Ueber die Degenerations- und Regenerationsvorgänge am Nerven nach Verletzungen, Beitr. z. path. Anat. u. z. allg. Path. **10**:321-393, 1891.

14. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, translated by R. May, London, Oxford University Press, 1928, vol. 1.

axis-cylinders where they were compressed by a mildly tight ligature, with resumption of full diameter below and with full capacity for regeneration when the nerve was sectioned distal to the ligature.

Though Lewis, Pickering and Rothschild [1] observed that the onset of paralysis following application of a pneumatic cuff is different in type from that caused by direct pressure on a nerve, our own observation on the remote result of paralysis induced by a short cuff or a tourniquet would give it close resemblance to, if not identity with, the results of prolonged localized pressure. Experimental data on the effect of localized pressure are, however, also meager.

Wier Mitchell [15] pointed out that rapid return of nerve function after its loss through compression indicated a "mechanical" interruption, as opposed to anatomic degeneration. He attempted to measure "the pressure needed to arrest the passage of nerve force" by experiments on rabbits and observed that if the sciatic nerves were compressed by a chamois leather bag containing mercury, a pressure of 20 inches (50.8 cm.) of mercury was necessary to cause loss of conduction, which failed gradually in ten to twelve seconds after the application of pressure. Restoration of conduction occurred within a similar period after release of pressure. He observed that fragmentation of the myelin sheath resulted when paralysis was thus induced. Grundfest [16] succeeded in eliminating the factor of anoxia inherent in Weir Mitchell's experiment by study of frog nerve immersed in oxygenated oil and totally enclosed within a pressure chamber. He found that a pressure of 1,000 atmospheres was necessary to abolish conduction in the nerve. At lower pressures (10,000 to 15,000 pounds [4,536 to 6,804 Kg.] per square inch [6.45 sq. cm.]), a condition of hyperexcitability resulted. In the production of clinical paralysis pressures of much less degree are effective over a period of minutes or hours. The part played by cessation of circulation then becomes the chief causative factor. Bentley and Schlapp [17] recently reported the results of acute experiments similar to our own, though electrical recording of nerve impulses was used as index of conduction and there was, therefore, no evidence of dissociation of paralysis in their observations. Further reference will be made to their work later. The following studies were directed toward determination of the relation of pressure to the onset and duration of paralysis and to establishment of the histologic nature of the "intermediate form" of partial lesion described by Erb.

METHOD

The experiments were carried out on cats anesthetized by intraperitoneal injection of pentobarbital sodium (30 mg. per kilogram of body weight). In order that the immediate effects of ischemia of a short segment of nerve might be determined, localized direct pressure was applied to a short segment of nerve in a number of preliminary acute experiments. In these experiments compression was applied directly to the exposed sciatic nerve trunk by a rubberized linen bag containing mercury under pressure (fig. 1). The brass base plate (fig. 1, at *B*) against which the bag compressed the nerve had rounded ends to lessen the chance of angulation of the nerve. The screw collar allowed the bag to be renewed easily and the distance from the base plate to be adjusted. The metal frame had a brass extension, not shown in the diagram, which allowed the whole instrument to be fixed rigidly in any position. The portion of the sciatic nerve in the midthigh was always used, due care being

15. Mitchell, S. W.: Injuries of Nerves and Their Consequences, Philadelphia, J. B. Lippincott Company, 1872.

16. Grundfest, H.: Effects of Hydrostatic Pressures on the Excitability, the Recovery, and the Potential Sequence of Frog Nerve, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, pp. 179-186.

17. Bentley, F. H., and Schlapp, W.: The Effects of Pressure on Conduction in Peripheral Nerves, J. Physiol. **102**:72-82, 1943.

taken to avoid damage to the entering vessels as the nerve was freed from connective tissue and mobilized. In other experiments tourniquets of various sizes were applied to the whole thigh and the nerves studied after an interval for recovery.

In short experiments the contraction of the tibialis anticus muscle was recorded by a spring myograph on smoked paper, the nerve being stimulated by a thyratron stimulator above and below the block. As the end point of failure was considered more significant than its onset, a sensitive myograph was used, with a stop to prevent greater excursion than approximately 25 per cent of maximal muscle tension. Sensation was estimated simply by the reaction of the lightly anesthetized animal to a thyratron stimulus applied to a peripheral sensory branch of the nerve.

For more prolonged observation of localized pressure a clip that could be applied to the nerve under sterile operative conditions was devised. This procedure, however, raised independent problems, which will be reported separately. We found the application of a tourniquet to the external surface of the limb more satisfactory for the study of persistent histologic change, and such changes as are described here were produced by the application of rubber tubing, the ends of which were clamped together by a hemostat, so as to compress the thigh just above the knee. The surface pressure exerted by the tourniquet was estimated by the height of a mercury column just sufficient to cause mercury to flow through a thin-walled rubber tube passing under the constricting band.

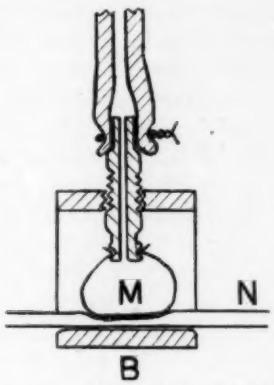

Fig. 1.—Diagram of mercury pressure bag, *M*, in relation to brass base plate, *B*, and the nerve, *N*.

IMMEDIATE RESULTS OF PRESSURE DIRECTLY APPLIED TO A NERVE TRUNK

The great variability in the effect of tourniquets and cuffs applied to the surface of the limb led us to investigate the results of pressure applied to the exposed sciatic nerve in the midthigh by means of a mercury bag. No attempt was made to follow the lesion for more than two hours after release of pressure, for the objective was to determine the relationship between pressure applied and latency of paralysis.

A repetition of Weir Mitchell's[15] mercury bag experiment disclosed that the sciatic nerve of the cat could tolerate a pressure of 20 inches (50.8 cm.) of mercury for more than two minutes without impairment of conduction or alteration of histologic structure, provided angulation of the nerve was avoided. The findings of Weir Mitchell, therefore, do not apply to the cat. A pressure of 30 inches (76.2 cm.) caused impairment of conduction to begin in twenty seconds, with almost complete failure in one hundred and twenty seconds. Recovery was complete in six minutes. At pressures of 48 inches (122 cm.) failure of conduction was complete at one hundred and sixty seconds. Sixteen minutes after release of the pressure there was complete recovery except that spreading of the toes was still feeble.

Subsequent experiments were designed to explain the effect of lower pressures, both in relation to latency of failure of conduction and to latency of recovery

when pressure was then immediately released. The relation between directly applied pressure and latency of failure of conduction is shown in graphic form (fig. 2).

It will be immediately apparent that there was considerable variation in the latency of failure of conduction at any one pressure, although in general the higher the pressure the briefer the latent period. A remarkable feature was the relative constancy in the resistance of the two sciatic nerves of the same animal. Thus, in 1 animal pressure of 30 cm. caused failure of motor conduction which was complete at twenty minutes in the right nerve and at nineteen and a half minutes

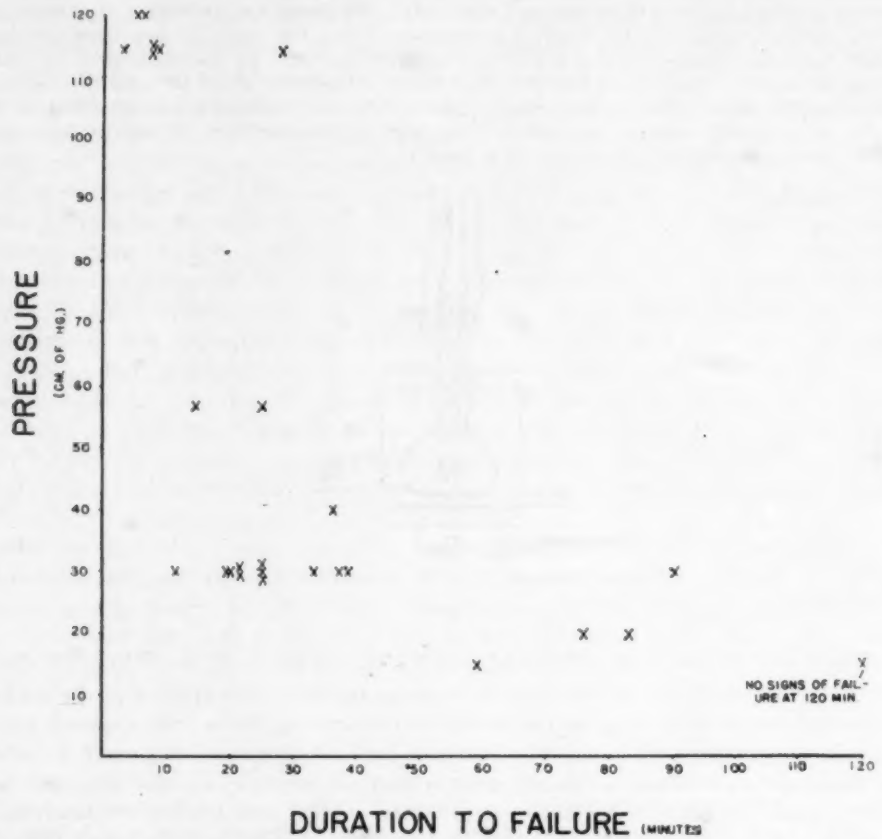

Fig. 2.—Graph showing relation of pressure to interval before onset of failure of conduction in acute experiments.

in the left nerve; in another animal the same pressure caused failure of conduction in twenty-five minutes in both the right and the left nerve. The extremes of variation in the latent period were not related to any difference in intracarotid systolic blood pressure, which regularly varied from 11 to 15 cm. of mercury. Great care was taken to obviate any kinking of the nerve by using a foot plate with rounded ends and arranging it so that it was wider than the distended bag (fig. 1). Some slight displacement of the nerve to one or the other side tends to occur as pressure is slowly increased, and it is possible that differences were related to slight variation in the extent of nerve subjected to pressure. No visible displacement was observed, however, in the major variations in the latent interval.

To examine the cause of prolonged resistance we determined the blood pressure by direct carotid manometric record and then, the bag still exerting pressure on the nerve, killed the animal and perfused the aorta with india ink in saline solution at a pressure just below the estimated systolic pressure. In cases of prolonged resistance it was found that, although the compressed segment was blanched, the perfusate had filled a large longitudinal vessel running through the compressed area in spite of the greater pressure of the contents of the bag. It is clear, therefore, that prolonged resistance to block may be due to relative protection of some vessels in the nerve. Since the sciatic nerve at the level of compression is made up of several large bundles, loosely held together by the epineurium, in which run the larger vessels, it was concluded that in such a case the escaping vessel had been protected from pressure by its lying in an interstice between the nonresistant bundles.

If this explanation is accepted for the variation in latency from case to case, it still remains to account for the shorter interval with greater pressure. A possible explanation might be that the delay in failure of conduction at the lower pressures is the result of incomplete ischemia due to diffusion of oxygen from vessels which are occluded only at the greater pressures. If this were so, there should be a minimum latent interval corresponding to the period of complete vascular occlusion. Further, the time of recovery might be expected to vary in proportion to the latent period, for the more complete the ischemia the less rapid should be the recovery. No such relationship was observed. Recovery tended either to begin immediately or to be much delayed, without relation to the pressure employed or to the latent interval of conduction failure. Thus after exposure to 56 cm. of pressure, with failure of conduction in twenty-seven minutes, recovery in 1 experiment began immediately on release. In another experiment, after failure in twenty-five minutes, recovery began six minutes after release. The duration of maintained pressure after failure of conduction should determine the rate and the degree of recovery, for, obviously, sufficiently prolonged pressure would result in necrosis. The results for short exposures were, however, again extremely variable. Thus a pressure of 30 cm. of mercury, with failure of conduction at twenty-four, nineteen and one-half, twenty-five, twenty, twenty-one and one-half and twenty-one and one-half minutes, was maintained for zero, twenty-six, twenty-five, thirty, thirty, forty and sixty minutes respectively after failure. The latent intervals of recovery were zero, thirty-six, two and thirty-seven minutes, forty-five seconds and one hundred and sixty-five and twenty minutes respectively. Thus the damage to conduction is extremely variable, probably also owing to uncontrolled escape of longitudinal vessels in the nerve, but possibly the result of a variable degree of oxygenation from the surrounding air. The compression bag and plate were kept at room temperature, which, however, did not vary greatly. In all these experiments the nerve remained fully excitable below the region of compression.

Though possibly a direct relationship could be demonstrated between duration of pressure and consequent damage if some completely fluid medium were used, the variability here found was present when the nerve was compressed against a soft bed of plasticene. As will be seen later, the variability is also present under more natural pressures.

A constant observation was a reduction in the latent period by repeated exposure to the same pressure. A pressure of 30 cm. of mercury, causing failure of conduction at sixty-five minutes, with immediate recovery on release, caused

failure at thirty-four minutes on a second exposure after a rest period of approximately ten minutes and at seven and a half minutes on a third exposure after a similar interval. In another animal 30 cm. of mercury, causing failure at thirty-seven minutes the first time, caused failure at five and a half minutes on the second compression and in five minutes on the third compression.

When failure of motor conduction was complete, sensory impulses conducted by the compressed segment of nerve were still unaffected, for peripheral electrical stimulation of a sensory branch caused a movement response in the animal as great as that from the same nerve in the opposite limb.

In none of these experiments did histologic examination of the nerve reveal any structural damage. Myelin sheaths, stained with osmic acid, and axis-cylinders, stained by the Bielschowsky method, were intact in all respects, even if a period of two hours was allowed to pass before the animal was killed and if no recovery had occurred in this time.

It is concluded, therefore, that variability in latency of failure of conduction in peripheral nerve as tested with a mercury bag is related to variability in the degree of ischemia thus brought about. The compartmented physical structure of a large nerve, like the sciatic, is such as to protect some of the longitudinal vessels from external pressure. The shorter latent period of failure of conduction with greater pressures suggests that diffusion from larger vessels results in lesser degrees of ischemia with lower pressure. The shortening of the latent period with repetition is characteristic of the behavior of peripheral nerve in anoxia (Lehmann [18]).

COMPARISON OF EFFECT OF LOCALIZED DIRECT PRESSURE AND EFFECT OF APPLICATION OF SPHYGMOMANOMETER CUFF TO SURFACE OF LIMB

The effect of application of the mercury pressure bag to the left sciatic nerve was compared with the effect of application of an inflated cuff to the right thigh. An infant's sphygmomanometer cuff folded to give a width of 6 cm. was used. With both bag and cuff at a pressure of 15 cm. of mercury there was complete failure of conduction in the left sciatic nerve (bag) at the fifty-ninth minute. The mercury bag was released forty minutes later. Recovery of conduction began immediately and was estimated to be complete in two minutes. On the right side (cuff) there was no failure of conduction after three hours and forty-five minutes of continuous compression.

When the pressures in the bag and cuff were at 30 cm. of mercury, conduction on the left side (bag) failed completely in thirty-three minutes and that on the right side (cuff) in twenty-two and a half minutes. On both sides the pressure was continued for forty minutes after failure. On the left side recovery commenced three minutes after release, and on the right side, in two minutes. The blood pressure of the animal was 150 mm. of mercury systolic (direct reading). Carmine gelatin injected into the aorta at a pressure of 150 cm. traversed a large epineurial vessel in the compressed area of each side in spite of the presence of the bag and the cuff at a pressure of 30 cm. of mercury. These procedures were repeated with another animal, with identical results.

These observations indicate that a pressure of 15 cm. of mercury in a sphygmomanometer cuff is not equivalent to a pressure of 15 cm. of mercury on the nerve. A small tube introduced alongside the nerve showed that the effective

18. Lehmann, J. E.: The Effect of Asphyxia on Mammalian A Nerve Fibers, Am. J. Physiol. **119**:111-120, 1937.

resistance at this depth was, in fact, considerably less than that under the cuff or the tourniquet, as the following tabulation indicates.

	Resistance to External Pressure, Cm. Hg	Resistance of Internal Pressure, Cm. Hg
Sphygmomanometer cuff, 6 cm. broad	20	12
Rubber tourniquet		
1 cm. broad	71	39
2 cm. broad	72	29
2 cm. broad	38	15
2 cm. broad	25	2.5

When, however, the external pressure exerted by the sphygmomanometer cuff was sufficiently high to cause an effective internal pressure, failure was more rapid than that with a corresponding local compression with the mercury bag. This was found to be the case even when an external cuff pressure of 30 cm. of mercury (failure in twenty-two minutes) was compared with a direct bag pressure of 40 cm. (failure in thirty-six minutes). This was probably due to the fact that the effective internal pressure produced by a 6 cm. cuff was exerted over a longer area of nerve than that compressed by the small linen bag.

The variability of the results in these experiments is not in accord with the constant failure of conduction, electrically recorded, which was observed by Bentley and Schlapp [17] twenty-five to thirty minutes after application of a 4 cm. cuff to the midthigh. These authors noted, however, that blood oozed when an artery below the compression was sectioned. They also observed failure of conduction to the ankle on stimulation either above or below a 4 cm. pneumatic cuff applied at a pressure of 24 to 28 cm. of mercury for thirty minutes. They noted that if the cuff pressure was maintained for three to four hours recovery was delayed one to two hours. In our experiments failure of conduction in the peripheral segment of the nerve did not occur in the experiments previously mentioned.

Bentley and Schlapp [19] concluded that diffusion of oxygen from surrounding tissues accounts for survival of the ischemic area of nerve. Their experiment showing shorter survival of nerve when the compressed area is wrapped in rubber membrane is, however, open to the objection that repeated anoxia lessens the latent interval to failure of conduction under identical conditions. We therefore prefer to regard the phenomenon as due to relative escape of interfascicular vessels.

PROLONGED PRESSURES AND RESULTING PARALYSIS

Attempts to apply the pneumatic cuff method of Lewis and his collaborators [1] to the hindlimb of the cat encountered difficulty, owing to the shape of the thigh of that animal. Only a narrow cuff (6 cm.) could be used. This was applied to the thigh of the anesthetized animal at a pressure of 50 cm. of mercury for two hours and six minutes. Twenty-four hours later there was paralysis of dorsiflexion of the foot and plantar flexion remained strong. There was no spreading of the toes, extension of the claws or placing. After forty-eight hours all movements had been fully recovered. In the opposite limb a pressure of 50 cm. of mercury for two hours resulted in a paralysis which had recovered completely in twenty-four hours. In another animal the same pressure, maintained for one hour, resulted in weakness (degree uncertain, owing to persistence of anesthesia) which had entirely disappeared in less than fourteen hours.

19. Bentley, F. H., and Schlapp, W.: Experiments on the Blood Supply of Nerves, J. Physiol. **102**:62-71, 1943.

These results from air pressure applied through a cuff may be compared with the following effects of tourniquets.

Summary of Data on Experiments on Paralysis Produced by Application of a Tourniquet to the Thigh *

No.	Tourniquet †	Width, Mm.	Pressure, Cm. Hg	Duration of Pressure, Min.	Duration of Paralysis	Day on Which Animal Was Killed	Block ‡		Histologic Changes §
							Motor	Sensory	
1	R	10	30	120	Complete for 9 days	16	—	—	L
2	R	12	45	45	Nil for 18 hours	14	—	—	L (sl)
3	R	13	45	60	Nil for 18 hours	14	—	—	L (sl)
4	R	13	45	75	Weak for 5 days	7	—	—	L (sl)
5	R	12	45	75	Nil for 18 hours	14	—	—	—
6	R	12	45	90	Nil for 18 hours	7	—	—	—
7	R	12	46	90	Nil for 18 hours	14	—	—	—
8	R	12	42	90	Nil for 18 hours	7	—	—	—
9	R	11	45	120	Complete for 19 days	19	P	—	L
10	R	10	45	120	Complete for 14 days	14	P	—	L (slD)
11	R	12	49	105	Weak for 7 days	7	P	—	L (sl)
12	R	10	50	120	Complete for 7 days	7	P	—	L
13	S	2	50	120	Nil for 18 hours	7	—	—	— (sl?)
14	R	11	60	120	Complete for 14 days	16	P	—	L
15	R	10	65	120	Complete for 2 days	16	P	—	L
16	R	12	70	120	Complete for 24 hours	1	P	—	L
17	R	10	75	120	Complete for 14 days	14	P	—	L
18	R	10	75	120	Complete for 9 days	16	—	—	L
19	R	12	75	123	Weak for 12 days	14	P	—	L
20	R	12	80	120	Complete for 24 hours	1	P	—	L
21	R	12	82	120	Complete for 14 days	14	P	—	L
22	R	10	100	140	Complete for 19 days	19	P	P	L+D
23	R	10	120	60	Complete for 24 hours	2	P	—	L
24	R	10	120	120	Complete for 48 hours	2	P	—	L

* For the sake of simplicity, the observations for the peroneal nerve alone are given.
† R means a rubber tourniquet was used, and S, a string tourniquet.
‡ P indicates paralysis.
§ L indicates a lesion; L(sl), a slight lesion, and D, degeneration.

It is at once apparent that the amount and duration of pressure necessary to cause persisting paralysis are extremely variable. Since the object of these experiments was to produce a lesion, the rate of recovery after the first day was carefully studied. The speed of recovery was slow, but also variable, so that in observations 14 and 15, which were made on the same animal, conduction on the right side, at a pressure of 65 cm. of mercury, began to recover on the second day, while recovery on the left side (at a pressure of 60 cm. of mercury) began only on the fourteenth day but was more rapid, and the two sides were equally strong on the sixteenth day.

In these tourniquet experiments the animal was allowed to survive for varying intervals. Before the animal was killed the nerve was exposed and stimulated under anesthesia induced with pentobarbital sodium. Except in 1 animal, in which muscular and nervous excitability below the block was also lost, it was noted that the cat still remained sensitive to a pinch of the toe, and this retention of sensation was verified with the animal under anesthesia by stimulation of a bared sensory branch below the lesion (e. g., the musculocutaneous or the posterior tibial nerve) and comparison of the reflex movements induced from the two sides or comparison of the reflexes thus induced with those produced by stimulation of a nerve of the forelimb. A protocol will suffice to illustrate these phenomena.

Experiment (Aug. 12, 1942): Tourniquets 1 cm. wide were applied at 75 cm. of pressure to the right thigh (17 in table) and at 45 cm. of pressure to the left thigh (10 in table), each for two hours.

Complete bilateral motor paralysis without sensory impairment to pinch of the pads on the dorsum of the foot persisted until August 26, when slight plantar flexion was noted on the right side. With the animal under anesthesia induced with pentobarbital sodium, the sciatic

nerves were then exposed. Sensory conduction appeared full on each side, as judged by stimulation of the musculocutaneous nerve. On each side the sciatic nerve, split into its two divisions at the level of the great trochanter, reacted to stimulation as follows:

Nerve	Side	Motor Response	
		Above Lesion	Below Lesion
Peroneal	Right	None	Good (90%)
Peroneal	Left	None	Weak (20%)
Popliteal	Right	Moderate (50%)	Full
Popliteal	Left	Very weak (5%)	Weak (20%)

The levels at which the change in response on the right side occurred are shown in figure 3.

The data on remaining significant tourniquet experiments are summarized in the table. In 1 experiment complete loss of excitability below the level of compression was produced, and there was then associated complete loss of sensation. In 7 experiments no paralysis was seen, and in these experiments low pressure was applied for a short duration except in experiment 13, in which a narrow string tourniquet was used. In all the others, paralysis without loss of reaction to a pinch of the foot (or to stimulation of a peripheral sensory branch at the

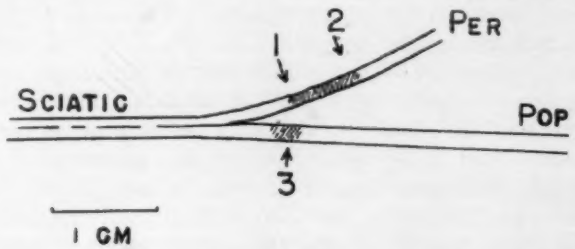

Fig. 3.—Drawing to scale showing relationship between histologic lesion (shaded) and the result of electrical stimulation in the experiment cited in the text. The arrow marked *1* indicates the most proximal point from which contraction of the post-tibial muscles could be secured. Distal to *2* the contraction was maximal. At the arrow marked *3*, on the popliteal nerve, there was an abrupt change from approximately a 50 per cent strength of contraction of the post-tibial muscles when the nerve was stimulated proximally to a 100 per cent strength of contraction when it was stimulated distally.

final exposure) was produced. Recovery was usually delayed until the fourteenth to the eighteenth day and then was unusually rapid, being clinically complete in two to four days. In some instances recovery began within twenty-four hours and was complete by the fourth day. In all instances in which full recovery was noted on clinical examination of the intact animal, subsequent direct electrical stimulation of the nerve under anesthesia revealed no defect in excitability above or below the level of compression. When weakness persisted at the time of exposure of the nerve under anesthesia, the excitability was greater distal to the level of compression than proximal. The damage to conduction from above the level of compression was always greater in the peroneal nerve than in the popliteal nerve. In stimulation the proximal ends of these nerves were always split down and immediately stimulated separately. The conductivity did not rise abruptly, but increased gradually over 5 to 10 mm. of nerve (fig. 3, between arrows *1* and *2*). In the animal in which all conductivity was lost (cat 22) in the peroneal nerve both above and below the level of compression, a differential still persisted in the popliteal nerve.

In an animal which had shown only slight weakness in spreading of the toes and in plantar flexion after compression with 10 mm. tourniquets for two hours at pressures of 55 and 65 cm. of mercury, respectively, repetition of compression with these tourniquets for the same period twenty-four hours after the first exposure caused no perceptible increase in the weakness.

This persisting nerve block differs considerably from a complete lesion, both in rate of recovery and in the persistence of electrical excitability in the distal segment after periods of as long as nineteen days. The muscles do not fibrillate under such circumstances, and atrophy is doubtful or absent. In 1 experiment complete degeneration of the peroneal nerve was produced on one side, and corresponding sections of the muscles confirmed the presence of atrophy only on this side, though pressure paralysis had been complete in the other nerve for nineteen days. Control experiments with crushing of the sciatic nerve in mid-thigh with a hemostat revealed that electrical excitability of the distal segment did not then return until eight weeks later. Such a lesion can also be produced when a tourniquet lesion is sufficiently severe.

HISTOLOGIC CHANGES ASSOCIATED WITH TOURNIQUET PARALYSIS

The nerves were examined routinely both by stains for myelin (osmic acid) [20] and for axis-cylinders (Gros-Bielschowsky).[21] In many cases Bodian's axis-cylinder stain, iron hematoxylin or a stain for fat (sudan III) was also used. In all cases in which the animal was killed on the same day as the experiment, even after compression for as long as two hours, or with a pressure as severe as 200 cm. of mercury, no change in myelin or in axis-cylinders was noted. The histologic changes that are characteristic of a lesion due to ischemic pressure appear within twenty-four to forty-eight hours and progress to about the tenth day. The following description applies to the lesion produced by tourniquet pressure for two hours; in every case motor excitability below the lesion was 75 to 100 per cent intact, and the gross reflex effects of stimulation of the sensory branch were unimpaired. The approximate amount of muscular contraction elicitable from above the lesion was 0 to 5 per cent.

Twenty-Four to Forty-Eight Hours.—At the end of this period, and for the next two to three days of complete motor conduction block, the only abnormality observed was slight edema of the compressed region, with a few scattered lymphocytes between the nerve fibers, and great thickening of the axis-cylinders where they were compressed (fig. 4 *A*). The increase in caliber of the axon began gradually and could be followed for 2 to 15 mm. Scattered vacuoles had appeared in the axis-cylinders, which also showed neurofibrillar condensation at the nodes of Ranvier. When such a nerve was stained with osmic acid or by some other myelin stain, the most obvious change was irregular vacuolation (fig. 4 *C*). The vacuoles appeared in the myelin of any part of the sheath. Other vacuoles were seen within the axis-cylinder, distending the sheath but not damaging the myelin. Close inspection of the nodes of Ranvier revealed a powdering of the myelin on the distal side of the cementing disk, but it was difficult to distinguish this from

20. Osmic acid method: Fix in 10 per cent concentration of solution of formaldehyde U. S. P. Cut block. Wash well in tap water for twenty-four hours and then in distilled water. Place in 1 per cent osmic acid for twenty-four hours. Wash well in tap water for twenty-four hours, embed in paraffin and section.

21. Gros-Bielschowsky method: Fix in 10 per cent concentration of solution of formaldehyde U. S. P. in saline solution; embed in pyroxylin and stain in sections, as detailed by one of us (Denny-Brown, D., in Carleton, H. M., and Lach, E. H.: Histological Technique for Normal Tissues, Morbid Changes and Identification of Parasites, ed. 2, London, Oxford University Press, 1938); counterstain with cresyl violet.

a staining artefact. The myelin sheath did not appear enlarged, and it appeared that the enlargement of the axis-cylinder was accompanied by some shrinkage of the sheath. These changes were observed over an extent of 10 to 20 mm. of nerve, the remainder appearing normal.

Seven Days.—At this interval after the application of pressure, the myelin appeared to have receded from the colorless cementing disk at the nodes of Ranvier for a distance of 0.01 to 0.04 mm. The change was most clear in the larger

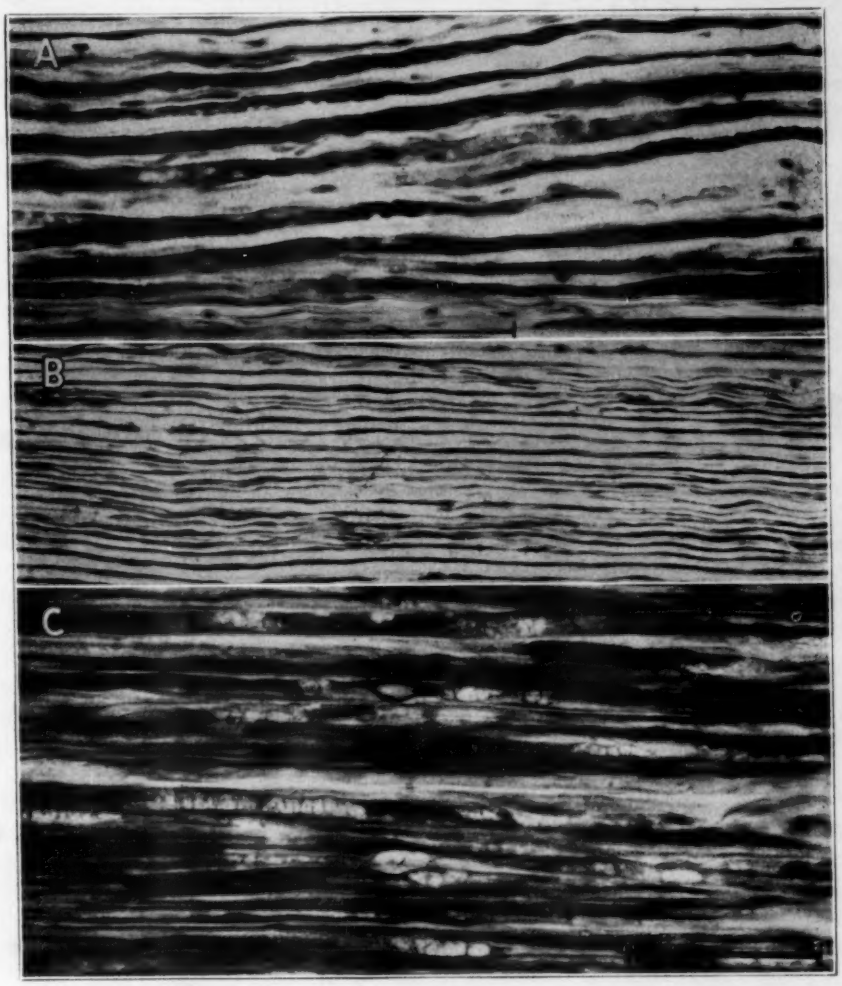

Fig. 4.—*A*, peroneal nerve; Gros-Bielschowsky method. Swelling of axis-cylinders after forty-eight hours of persistent motor paralysis following application of tourniquet at a pressure of 120 cm. of mercury for two hours. The ruled line at the bottom of this photomicrograph, and at that of *C*, is equivalent to 0.1 mm.

B, control nerve; same method and magnification.

C, peroneal nerve; osmic acid stain. Vacuolation of myelin twenty-four hours after application of tourniquet at a pressure of 80 cm. of mercury for two hours, with persisting complete paralysis.

fibers but was also noted in many of the smallest myelinated fibers. Axis-cylinder stains of the nodes of Ranvier affected in this way revealed great thinning of the

axis-cylinder through and distal to the node, corresponding to the extent of loss of myelin, with irregular unraveling of the neurofibrils. The vacuoles were no longer present. The remaining lengths of axis-cylinder were greatly swollen. The myelin distal to the node was coarsely granular, and the whole myelin sheath was ballooned out; the actual thickness of myelin, however, was reduced. The Schmidt-Lantermann incisures in the intervening region were widened and more prominent. These nodal changes were noted over a length of 10 to 20 mm., on both sides of which the nerve was of natural appearance.

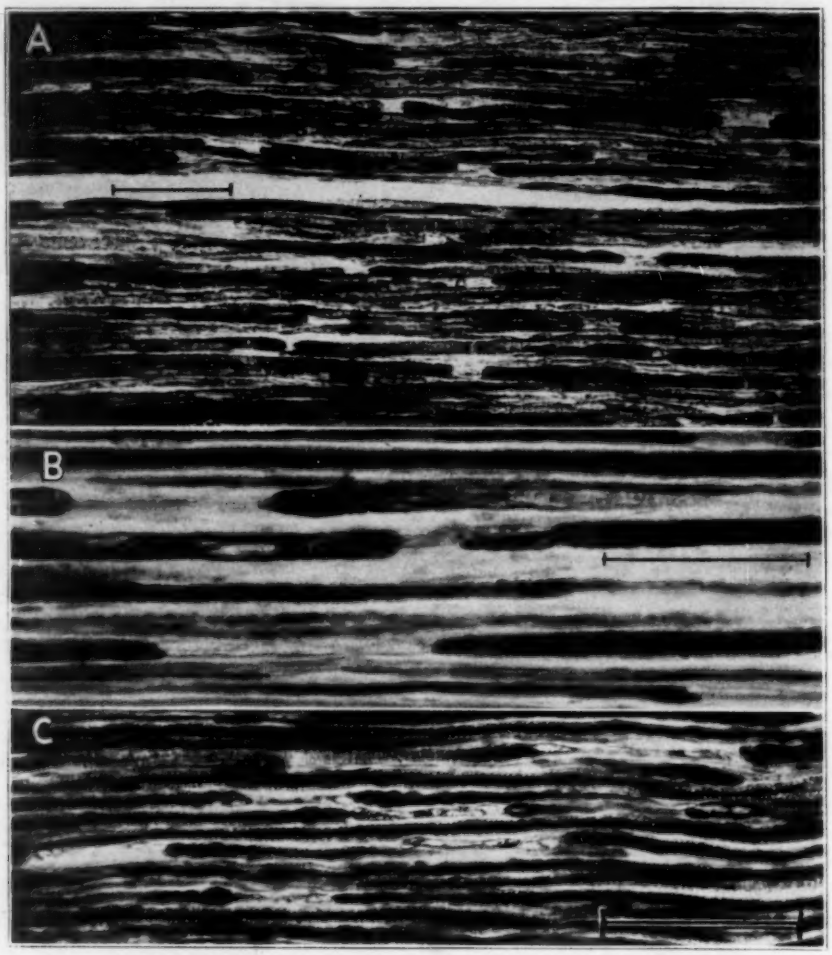

Fig. 5.—*A*, peroneal nerve; osmic acid stain. Gaps at nodes fourteen days after application of tourniquet at a pressure of 75 cm. of mercury for two hours, with persisting paralysis (same experiment as that for which diagram is shown in figure 3). The ruled line in *A*, *B* and *C* is equivalent to 0.1 mm.

B, peroneal nerve; osmic acid stain. Gaps at the nodes nineteen days after application of tourniquet at a pressure of 45 cm. of mercury for two hours (severe block).

C, popliteal nerve; osmic acid stain. Same experiment as that in which section shown in *B* was taken; minimal lesion (25 per cent block).

Two Weeks.—If this interval was allowed to elapse without improvement in the motor paralysis, the same changes were observed, and their persistence for

this period made it clear that they were not part of wallerian degeneration. The most proximal alteration was still the loss of myelin at the nodes of Ranvier, as already described, except that the gap in the myelin was in general more clearcut (figs. 5 and 6) and no granules remained. In Gros-Bielschowsky preparations many axis-cylinders failed to stain at the node of Ranvier (fig. 7) in the region of the conduction block, though the protoplasmic outline was visible (fig. 8 *A* and *B*). In others a slender, refractile, nonargentophil thread connected the thick ends of the axis-cylinders (figs. 8 *B* and *C*). More distally the gaps in the myelin sheath suddenly widened, a long strand of axis-cylinder covered by a thin myelin sheath remaining (fig. 9). The nuclei of the Schwann cells appeared not to react, for no evidence of mitosis was seen in them. There was, however, great infiltration with macrophages, some of which now regularly embraced the bared section of axon (fig. 8 *A*). The widening of the node appeared to be chiefly at the expense of the next distal myelin segment, which began suddenly with a rounded bead, often staining densely with osmic acid (fig. 9 *A* and *C*). The axis-cylinders stained feebly, or not at all, where the myelin was defective, so that at this level the contrast between the alternating thin threads and the broad remaining bands of axis-cylinders was remarkable (fig. 7 *C*, *D* and *E*). Irregularity and occasional vacuolation of the short, thickened segment of the axis-cylinder were evident in the region of greatest damage. Collateral appendixes of the axon appeared at intervals (fig. 8 *A* and *C*). The nerve was here edematous, with fibers widely spaced; the mesodermal elements were swollen (figs. 7 and 8), and lymphocytes were scattered through the endoneurium, sometimes in small clumps. This alteration of thinned and thickened portions of the axis-cylinder was now noted for 1 to 2 cm. The maximal diameter was approximately twice that seen in normal nerve. Farther distally the thinned segments shortened rapidly, and the thick segments lengthened and resumed normal caliber, with restoration of normal nodes of Ranvier.

For about 1 mm. distal to the last gap in a node of Ranvier, the myelin sheath was unduly swollen on either side of each node (fig. 6 *E*). Below this level no histologic defect was present. In some animals the axis-cylinders and the myelin below the lesion, while normal in other respects and conducting impulses for full contraction, showed short beaded alterations in caliber up to their junction with intact motor endings. A possible reason for this beading was the peripheral vascular stasis at the time of application of the tourniquet. Its absence in some animals and its presence above the lesion in some others, together with the lack of disturbance in function associated with it, seem to us to indicate that such beading is of little significance.

The extent of the lesion in a typical experiment and its correlation with the observed excitability below the lesion are shown in figure 3. Full conductivity was regained just above the most distal myelin gaps. The electrical stimulus may have been effective for 1 to 2 mm. beyond the point of application of the electrode, owing to spread of current.

Longer Intervals.—When the paralysis had persisted sixteen to nineteen days, the alternate thinned and thickened portions of the axis-cylinders, the edema and the mesodermal cellular reaction were still conspicuous. They were present over a length of 1.5 cm. of nerve when recovery in conduction had occurred rapidly in the previous two days. The alternate decrease and increase in caliber of the axis-cylinders and in myelin were noted, as before. The thin connecting link was more often thinly myelinated after fourteen days, or when recovery of conduction had been early, than when the animal had been killed early with still a complete block (figs. 5 *C* and 6 *B*). At the proximal extremity of the lesion

the only change in myelin was the widening of the node of Ranvier. Distal to the lesion the normal caliber and the normal nodes of Ranvier were resumed.

These changes might be present for fourteen to nineteen days without any histologic evidence of degeneration. In other cases there was greater severity of the lesion, and varying degrees of degeneration, with characteristic ellipsoids and

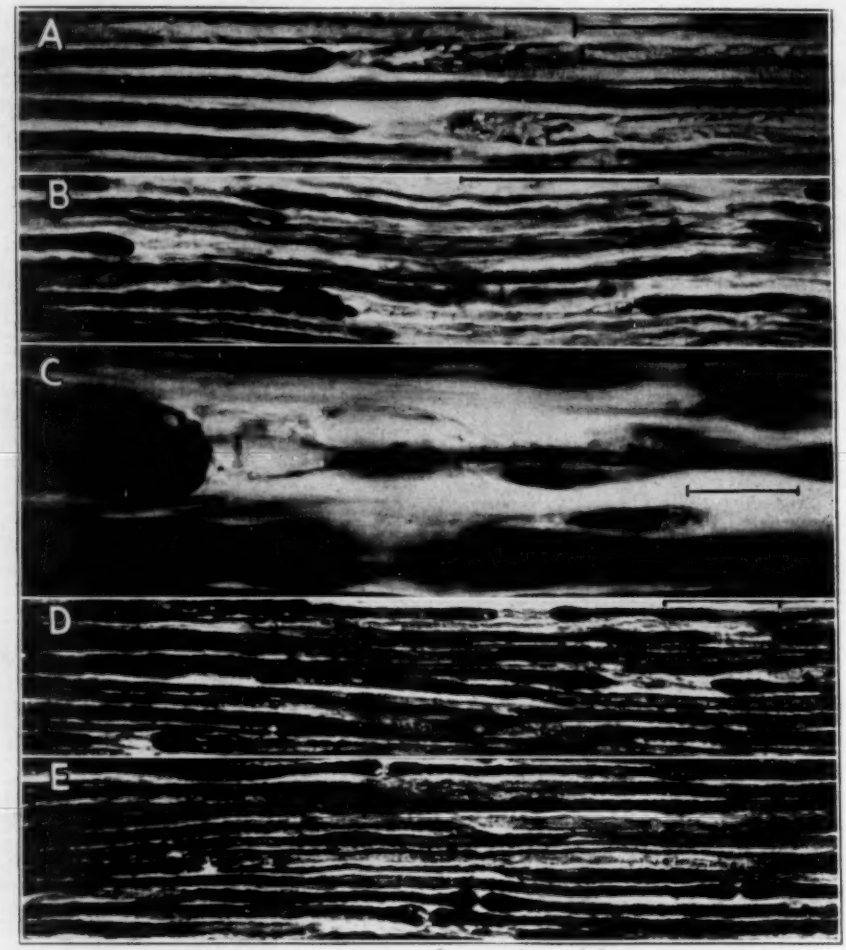

Fig. 6.—*A*, peroneal nerve; osmic acid stain. Changes in myelin fourteen days after application of tourniquet at a pressure of 45 cm. of mercury for two hours, which did not leave any persisting paralysis. The ruled line in *A* and *B* is equivalent to 0.1 mm.

B, popliteal nerve, from the same experiment as that in which section shown in figure 5 *B* was taken, illustrating the myelin covering a long gap.

C, peroneal nerve; sudan stain for fat; oil immersion lens. Changes at node after application of tourniquet at a pressure of 82 cm. of mercury for two hours, with persistent paralysis for fourteen days. The phagocyte near the sound fiber has many fat granules in the cytoplasm. The ruled line is equivalent to 0.01 mm.

D, peroneal nerve, from the same experiment as that from which the section shown in *C* was taken; osmic acid stain. Distal extremity of the lesion showing gaps in the myelin sheath. The ruled line is equivalent to 0.1 mm.

E, section 1 mm. distal to that shown in *D*, illustrating transition to normal nodes and myelin sheaths distal to the lesion. Note swellings at the nodes. Magnification same as that used in *D*.

fragmentation, accompanied the alternating increase and decrease in caliber of the remaining sound fibers. When degeneration was present below the lesion, the excitability of the nerve in this region was impaired in proportion. In a case of severe block, in which both sensation and neuromuscular excitability were lost, a

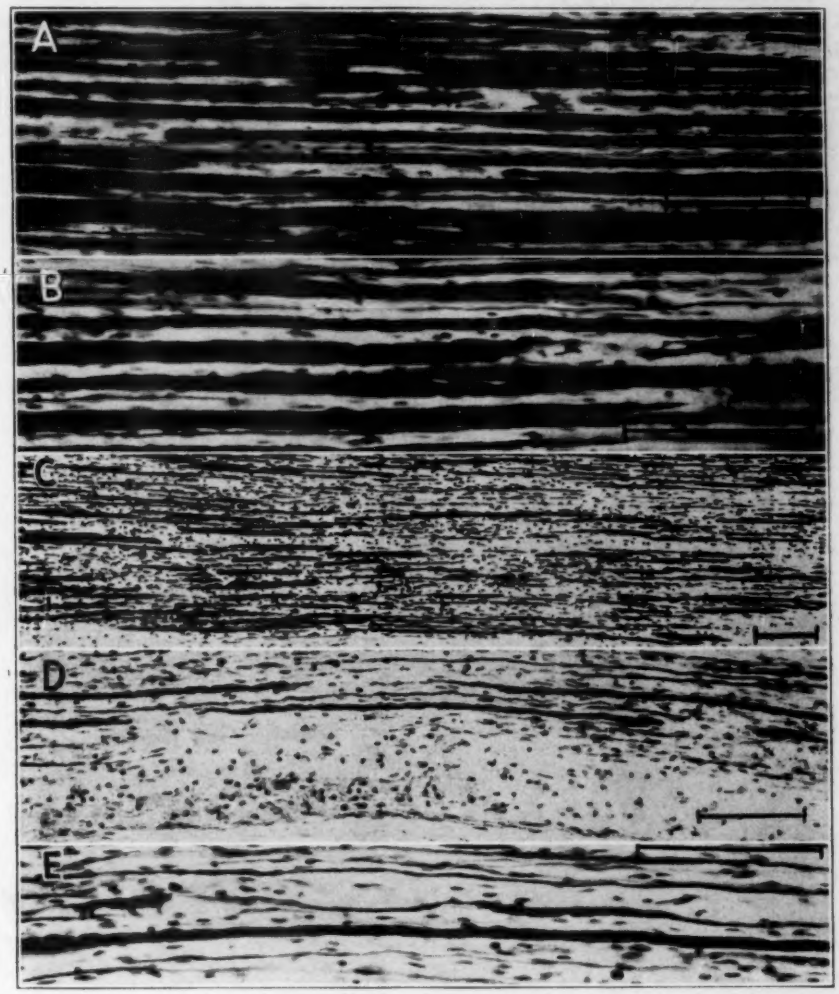

Fig. 7.—*A*, peroneal nerve, from the same experiment as that in which the sections shown in figure 6 *D* and *E* were taken; Gros-Bielschowsky method. Damage to axis-cylinders at nodes and lymphocytic infiltration, 6 mm. proximal to the area of change in myelin shown in figure 6 *D* and 5 mm. distal to the area of nodal change illustrated in figure 6 *C*. The ruled line in the right lower corner, and in all other portions of this figure is equivalent to 0.1 mm.

B, peroneal nerve, just proximal to the area of change in myelin illustrated in figure 5 *B*; Gros-Bielschowsky method. Change in axis-cylinders at damaged node and irregularity of staining of fine fibers.

C, popliteal nerve; Gros-Bielschowsky method. Appearance of alternate thick and thin segments of the axis-cylinder in a severe lesion nineteen days after exposure to a pressure of 100 cm. of mercury for two hours.

D, section of the same specimen of popliteal nerve as that shown in *C*; Gros-Bielschowsky and cresyl violet stains. Two myelin gaps in one fiber and cellular reaction.

E, higher magnification, showing alternate thickening and thinning illustrated in *C*.

short region in which the caliber of the fibers showed alternating increase and decrease passed into one of complete degeneration more distally.

In 3 animals pressure which had caused no observed weakness or paralysis after eighteen hours (recovery from anesthesia) had caused alternating increase

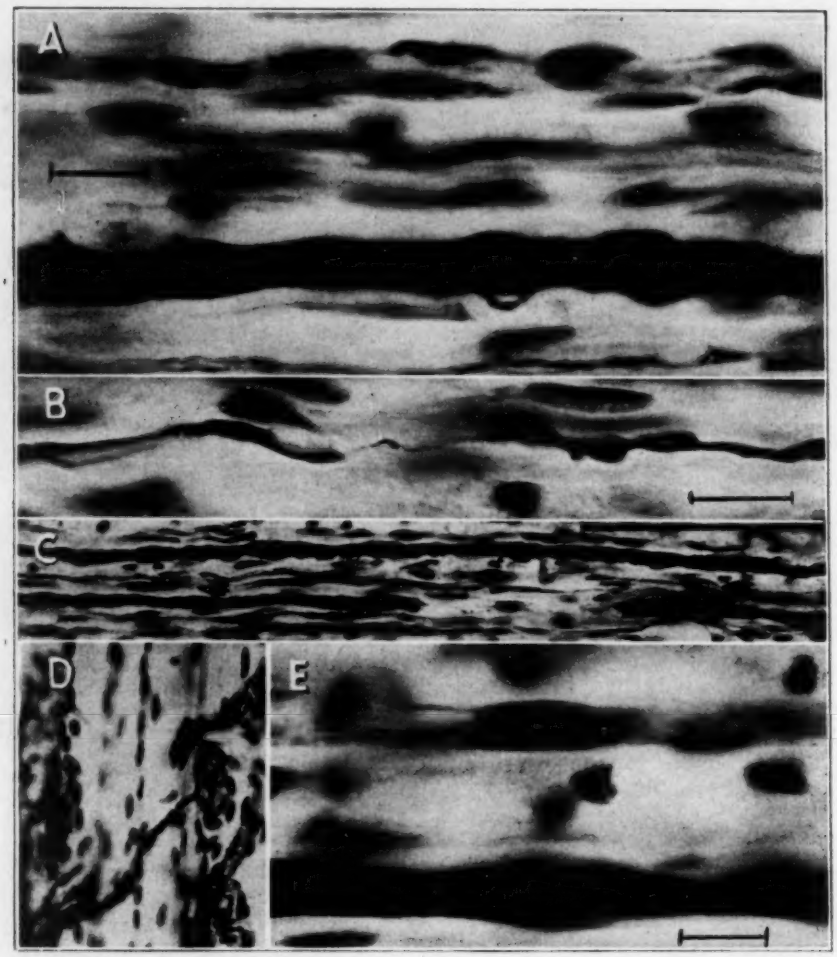

Fig. 8.—*A*, popliteal nerve; Gros-Bielschowsky and cresyl violet stains. High magnification of a severe lesion persisting nineteen days after application of tourniquet at a pressure of 100 cm. of mercury for two hours, showing collaterals on a thick segment of axis-cylinder and above it two thick, but unstained, segments, with enveloping nuclei. Below is an altered nonmedullated fiber. The ruled line is equivalent to 0.01 mm.

B, section from the same nerve as that shown in *A*, indicating the appearance of an argentophil thread in a small medullated fiber connecting two irregularly thickened segments. The ruled line is equivalent to 0.01 mm.

C, higher magnification of the gap on the right side of the fiber illustrated in figure 7 *D*, showing extremely fine, wavy filament connecting two thickened axis-cylinder segments. The ruled line is equivalent to 0.1 mm.

D, normal motor endings, characteristic of a large number examined in muscle paralyzed by a pressure lesion for sixteen days.

E, section from the same nerve as that illustrated in *A*, showing argentophil streaks in a thickened, but otherwise unstained, axis-cylinder, with enveloping nucleus. A phagocyte with granular cytoplasm lies between the stained and the unstained fibers. The ruled line is equivalent to 0.01 mm.

and decrease in caliber of the nodes in one or two fiber bundles, the rest being unaffected. In cases in which recovery of function occurred in the first few days there was slight widening of nodes over an extent of 2 to 3 mm. of nerve, which was observed to persist as long as fourteen days, and probably longer. When conduction had commenced to recover within seven days, the changes were also usually restricted to the immediate myelin bordering the node, with gaps of 0.04 mm. or less, and such changes were observed over only 2 to 10 mm. of nerve.

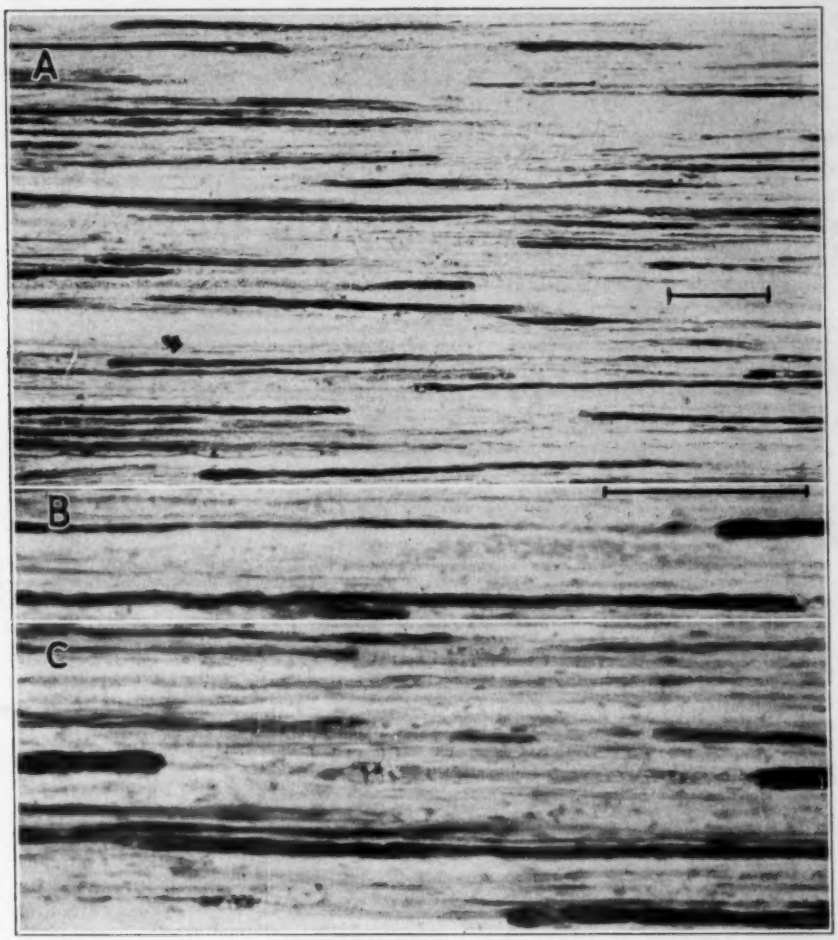

Fig. 9.—*A*, popliteal nerve; osmic acid stain. Section just proximal to the area of change shown in figure 7 *C*, illustrating the characteristic thinning and thickening of myelin segments in a severe lesion of nineteeen days' duration. The ruled line is equivalent to 0.1 mm.

B and *C*, higher magnification of the section shown in *A*. The ruled line is equivalent to 0.1 mm.

Increase in severity of the lesion was therefore seen both in greater width of the myelin gap and in a longer section of nerve involved.

It is clear, therefore, that the transient forms of pressure paralysis constitute a lesion of the nerve fibers in continuity. There is loss of conduction accompanying a structural change in the nerve fiber. The most obvious change is the widening of the node of Ranvier, due to loss of myelin. This occurs in all large

fibers, and in most small fibers in any section at the level of maximal lesion. A characteristic low power view of an osmic acid preparation is shown in figure 5 *A*. Every node in the section is affected. The change in caliber of the axis-cylinder is so closely associated with damage to the myelin that it is not possible to state which is primary. Even after only twenty-four hours of paralysis, when the axis-cylinder is already swollen, the myelin at the node of Ranvier, normally thin and a little irregular, shows vacuolar change (fig. 4 *C*). Nonmedullated fibers, however, also show thinned segments and beading in the affected

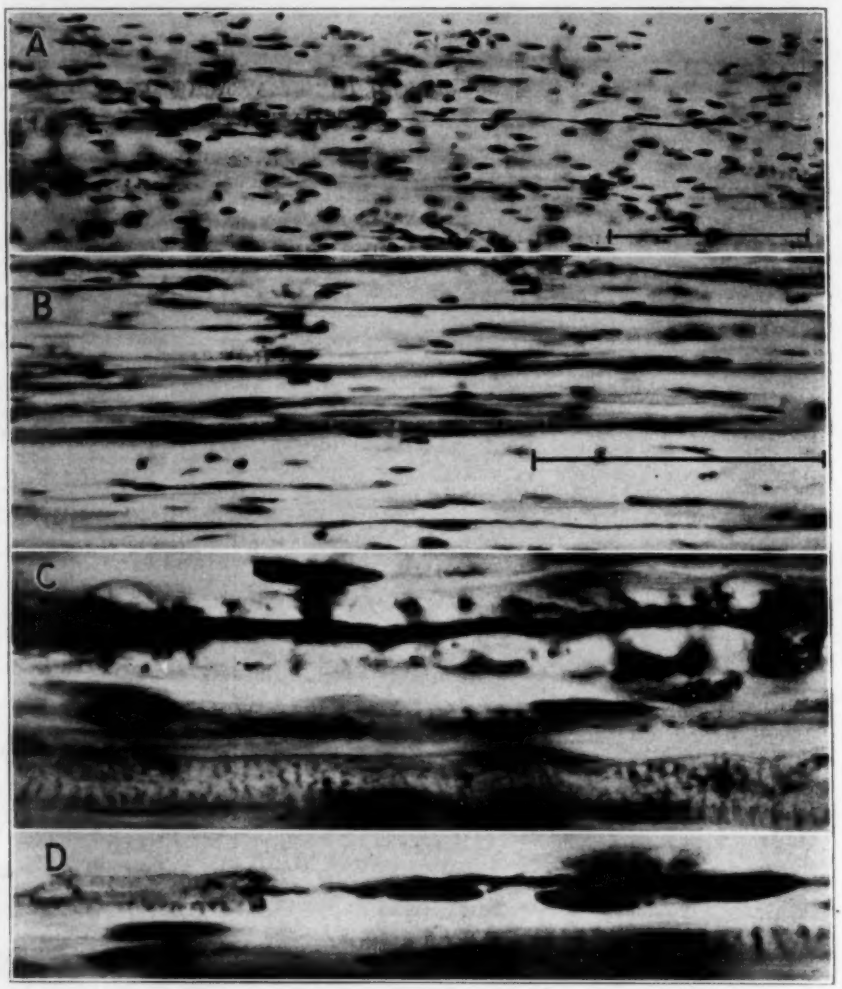

Fig 10.—*A*, popliteal nerve (iron hematoxylin stain), showing staining of a bared segment of axis-cylinder sixteeen days after application of pressure of 65 cm. of mercury for two hours. The ruled line in *A* and *B* is equivalent to 0.1 mm.

B, peroneal nerve (iron hematoxylin stain), showing staining of segments of the axis-cylinders, as compared with a sound myelinated segment in the center and a damaged node at the right upper corner.

C, from the section in *A* (oil immersion lens), showing staining of damaged axis-cylinder with iron hematoxylin above and normal myelin below.

D, from the section in *C*, illustrating the transition from bared axis-cylinder to myelinated segment.

zone (figs. 7 *B* and 8 *B*), and some vacuolation is present in finely medullated fibers in the early stages. Resumption of function appears to accompany the more general reappearance of a small, thin coating of myelin over this intervening filament, though this is seen in some gaps at all stages. At the level at which full excitability appears, and in the whole lesion for two weeks or more after recovery of conduction, the lesion differs little from that of a totally blocked nerve.

In severe lesions a cementing disk is not always visible in the myelin gap. Such interruptions are then usually opposite a Schwann nucleus (fig. 7 *D* and *E*), i. e., in the middle of the myelin segment, as well as at the node of Ranvier. Ramón y Cajal [14] (page 76) described widening of the node of Ranvier in the first two days of wallerian degeneration and the slower formation of a gap opposite the Schwann nucleus. Such changes are, then, a prelude to the fragmentation of the myelin segment. He spoke of "retraction" of the myelin, for he evidently seldom observed fatty granules. A complete pressure block of the nerve can exist for nineteen days without evidence of the usual degeneration of myelin to form ellipsoid bodies. The disappearance of myelin in the naked gaps is, however, a true dissolution, with the appearance of large vacuoles, the contents of which do not stain with osmic acid, sudan III or hematoxylin (fig. 6 *C*). The vacuoles shrink rapidly in the first seven days, leaving the Schwann sheath closely applied to the bared argentophobe axon, but are to be noted at some nodes after fourteen days. Oval mononuclear cells closely embrace the still thickened axoplasm. These have the appearance of Schwann cells, with an oval pale nucleus lying obliquely to the axon, but the absence of a nucleolus, the lack of mitosis in other Schwann cells and the abundance of wandering tissue cells lead us to identify them as histiocytes. A phagocyte filled with fat granules commonly lies near the gap in the myelin, but not closely applied to it (figs. 6 *C* and 8 *E*).

The persistence of lengths of axis-cylinder which will not take silver stains is a remarkable feature. It was observed that this region of the axis-cylinder stains deeply with iron hematoxylin, so that a section of the block stained in this way and lightly decolorized gives a picture the reverse of that of a silver stain (fig. 10). This astonishing change in the property of the surviving axis-cylinder is of considerable interest, for it indicates some relation between argentophil property and conductive function.

A further characteristic of this intermediate lesion is the slight degree or absence of disorder of sensation, so far as sensation can be judged in the experimental animal. This is true of the acute lesion (bag experiment), as well as of the chronic lesion (tourniquet experiment). In the days immediately following the establishment of an intermediate lesion there appears, in fact, to be some hyperesthesia in the form of an exaggerated withdrawal of the limb from light contact. The histologic changes in this intermediate type are certainly most obvious in large nerve fibers, but similar changes, i. e., widening of nodes and beading, are also present in small medullated fibers, and beading is noted in nonmedullated fibers. The apparent sparing of sensation would have a possible explanation on a basis of fiber size in that the tests on experimental animals fail to distinguish touch from pain were it not that in 2 clinical examples of tourniquet paralysis in man seen by one of us (D. D.-B.) there has been no disorder of touch or pain after the first few hours, whereas complete motor paralysis had persisted for two and four weeks respectively, without reaction of degeneration. In our experiments we were unable to find any size of fiber which was consistently unaffected.

The difficulty in identifying the exact length of nerve submitted to pressure by the tourniquet experiment leads to difficulty in estimating the exact degree of

spread of the lesion proximally and distally from the zone of pressure. The latter is being determined in other experiments on the production of lesions by direct pressure on the nerve, and the results will be reported later. The tourniquet experiments reveal, however, that the lesion can extend as much as 1 cm. below the original area of compression.

It would manifestly also be of interest to determine the time taken for complete restoration of histologic structure. The tourniquet method is not, however, suitable for this, owing to uncertainty of the degree of purity of the original lesion when more than three weeks is allowed for recovery, and products of degeneration are less easily recognizable. We have observed the presence of notable changes in caliber eight weeks after a localized pressure lesion.

CHANGES IN MUSCLE FIBERS

The intermediate degree of pressure lesion is found to be accompanied by paralysis of muscle, often complete, without loss of faradic excitability and without fibrillation. It is evident that the lesion blocks natural nerve impulses and those artificially stimulated at the frequency used (50 to 60 per second). We have not yet carried out experiments to determine whether conduction of impulses of slower rates or of altered impulses is possible. The muscles were observed closely during stimulation, and no evidence that even occasional full impulses reached the muscle was obtained. Section of the muscle, as compared with a corresponding section from the control leg when degeneration had occurred, revealed that atrophy was less than that on the degenerated side. The nerve endings were unaffected (fig. 8 *D*). The lesion, therefore, demonstrates that anatomic continuity of nerve, not receipt of impulses, prevents atrophy and fibrillation of muscle.

COMMENT

The experiments reported in this paper concern both the immediate and the remote aspects of the effect of pressure on nerve. The damaging effect of a tourniquet or a constricting cuff placed around the limb is, as Lewis, Pickering and Rothschild [1] had so clearly shown in studies of the onset of paralyses in human experiments, primarily traceable to the segments of nerve directly compressed. The effect of the vascular stasis peripheral to the cuff or tourniquet has a very slow onset at room temperature, as Lewis and his collaborators also clearly demonstrated, and does not complicate experiments of two hours' duration or less.

The work of Grundfest [16] had clearly shown that pressure in itself had no direct effect on the excitability or conductivity of nerve within the ranges of clinical possibility. Compression of mammalian nerve without angulation must be effective through the related ischemia. Our experiments have shown a great variability in susceptibility of nerves to externally applied pressures. This variability is clearly related to variable gradients of pressure in the tissues, where anatomic structure provides compartments of differing rigidity. Our experiments with direct pressure exerted on the bare nerve by a mercury bag indicated that small blood vessels can even then remain patent in the interstices between blanched nerve bundles.

These anatomic irregularities must be largely eliminated by pressure exerted over a sufficient length of nerve. The relative constancy of time which elapsed before paralysis occurred in the experiments of Lewis, Pickering and Rothschild [1] on the human arm, together with old observations on the value of a wide sphygmomanometer cuff in the measurement of blood pressure, confirms this assumption. Nevertheless, the common causative factors in pressure lesions in nerve are

applied over a short extent of nerve, and their variability in production of lesions must find explanation in variable anatomic factors.

It might be expected that ischemia would be an "all or none" effect. There is, however, a general increase in the speed of failure of conduction of nerve with increase in pressure, indicating that partial degrees of ischemia exert an identical effect over a longer period. Moreover, at all the pressures employed by us the failure of conduction was selective in that conduction of motor impulses failed before transmission of sensation.

The persistence of the nerve block for days or weeks requires not only that the ischemia persist for about two hours, but that it should be relatively complete. Thus tourniquet paralysis requires greater pressure than is needed to obstruct the main vessels to the limb. After pressure for two hours or less sensation may be impaired, but has recovered in a few hours, and the block is then usually one of motor conduction only, lasting two to eighteen days. Sufficiently intense pressure for two hours produces a more prolonged paralysis of both sensation and muscular power, lasting six to eight weeks before the first signs of recovery. The peripheral portion of the nerve is then observed to be degenerated, and the muscles are atrophic and fibrillating.

The more transient type of motor paralysis, with sparing of sensation, is evidently that described by Erb [5] in man, with what he termed an "intermediate type of reaction of degeneration," for the electrical excitability of the nerve below the lesion is retained well beyond that of a degenerating nerve. Our histologic studies have revealed that this is a disorder of conductivity of nerve without loss of anatomic continuity in the nerve fibers. This lesion is of considerable interest. The damage takes the form of intermittent attenuations of the axis-cylinder and myelin sheath. The points of least resistance are the nodes of Ranvier and the region opposite the Schwann nucleus. The early observations (twenty-four to forty-eight hours) on the lesion indicate an extensive disturbance of the protoplasm of the axis-cylinder, seen as swelling and vacuolation throughout the region subjected to compression. At this stage edema and lymphocytic infiltration have already appeared in the endoneurium. The emphasis then shifts to the myelin, which at the nodes of Ranvier becomes granular, fissured and vacuolated, with exposure of the bared or thinly covered axis-cylinder. Migrating histiocytes become filled with fat granules. The bared sector of axis-cylinder loses much or all of its affinity for silver stain and acquires an affinity for iron hematoxylin. These changes extend over a distance of 0.5 to 3 cm., beyond which normal structure is usually resumed. At the height of a severe lesion the nonmedullated segments are as long as the remainder of the myelin. Beyond this stage of severity, in which the nerve has the appearance of alternating thin and thick fibers, the thin connecting axis-cylinder presumably breaks. Once continuity is lost the distal segment degenerates, though the proximal part of the lesion has the characteristically widened nodes. The stage of the lesion short of degeneration may persist as long as nineteen days, by which time recovery of conduction is beginning to occur. Most of the thin connecting links of axis-cylinder have then acquired a fresh, thin covering of myelin. Recovery of conduction is rapid and complete, but restoration of histologic structure appears to require more than two months. We are uncertain whether it is ever complete. Throughout this period the lesion is associated with obvious mesoblastic reaction and edema, both in the endoneurium and in the epineurium. The mesoblastic reaction is itself of great interest, for lymphocytes and macrophages are mobilized and edema has occurred within twenty-four hours. The mechanism for this reaction is a matter for speculation, but it is clear that there is usually no visible damage to the blood vessels.

Under pressure the nerve is undoubtedly stretched. We have considered the possibility that the thin node of Ranvier then becomes greatly attenuated and that the thinned segment subsequently seen represents this alteration. The sheaths do not, however, reveal any such immediate change, even after extreme pressures and complete failure of conduction. The characteristic alternate thinning and thickening of the fibers develops in the course of ten days. Further, the first stage of disappearance of myelin at the node of Ranvier is identical with the first stage of degeneration of myelin distal to the lesion after nerve section, described as "retraction of myelin" by Ramón y Cajal,[14] this change then being preliminary to general fragmentation of the myelin sheath. We have presented evidence that the disorder is a dissolution of myelin, and not retraction.

The intervention of an extremely thin segment of nerve with a narrow myelin sheath between two segments of wider diameter constitutes a characteristic lesion. It closely resembles the lesion which Gombault [22] observed in 1880 in cases of lead paralysis and named "segmental periaxial neuritis." It was subsequently observed with other forms of neuritis, particularly beriberi (Pekelharing and Winkler [23]), and was produced experimentally in guinea pigs by intoxication with lead and with arsenic by Stransky.[24] The latter investigator observed that restoration of a thin myelin sheath began in the bared segment four weeks after cessation of the administration of lead. He expressed the belief that the segmental degeneration began opposite the Schwann nucleus, with increase in the corpuscles of Erzholz, and many investigators have pictured loss of myelin over one whole segment. As we have indicated, the ischemic lesion begins at the node of Ranvier, and the corpuscles of Erzholz are not increased, though secondary interruptions of the sheath occur opposite the Schwann nucleus at a later stage. The lesion is not so extensive as that in segmental periaxial neuritis. The phenomenon of ischemic lesion, as observed by us, will give added interest to the search for partial damage to nerve in other kinds of neuritis.

The lesions produced in our experiments were maximal just below the bifurcation of the sciatic nerve, at which level a tourniquet placed on the lower portion of the thigh of the cat exerts the greatest pressure. The peroneal nerve invariably showed greater defect in conduction and more severe histologic change than the popliteal nerve. The difference in the liability to damage of the two nerves in man to apparently similar injurious agents is a common clinical experience (Wilson [25]). Besides the obvious difference in size of the two nerves, the peroneal division is usually in the form of one major bundle, so that its vessels have less protection than those of the popliteal division, which lie in the crevices between the bundles. This anatomic difference may certainly account for the difference in lesions caused by pressure.

The escape of more distal segments of the nerve indicates that the peripheral stasis of circulation has little or no part in the production of the lesion, though with longer periods and at higher temperatures such an effect might be expected. We believe that the peripheral stasis in the nerve bundle is responsible for the extension of the lesion a few millimeters below the level of original compression. We are less certain of the cause of beading of the peripheral segments of the axis-cylinder and myelin. This phenomenon was inconstant and when present did

22. Gombault: Contribution à l'étude anatomique de la névrite parenchymateuse subaiguë et chronique; névrite segmentaire peri-axile, Arch. de neurol., Paris **1**:11-38, 1880.

23. Pekelharing, C. A., and Winkler, C.: Beri-Beri, Edinburgh, Young J. Pentland, 1893.

24. Stransky, E.: Ueber discontinuerliche Zerfallsprozesse an der peripheren Nervenfaser, J. f. Psychol. u. Neurol. **1**:169-199, 1902.

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not interfere with conduction. Its inconstancy leads us to relate it provisionally to the stasis of the peripheral circulation and therefore to anoxia of a slightly different type from that of the localized ischemia. An attempt was made to induce ischemic lesions in nerve directly by ligation of all the vessels to the sciatic nerve in the cat (pudendal, sciatic and popliteal tributaries). No defect in conduction could be demonstrated in 3 such experiments. Injection of the aorta with india ink when the animals were killed two weeks later revealed a complete longitudinal circulation in the nerve from vessels above and below the lesion. In the nerves from these animals patchy areas of swelling of the axis-cylinders with vacuolation were observed which were identical with the earliest stage of ischemic lesions produced by the tourniquet except that these changes persisted for periods of twelve to fourteen days. Bentley and Schlapp [17] also showed the persistence of conductivity by electrical recording methods when lateral branches entering the sciatic nerve in the cat were ligated. The histologic changes observed in our experiments suggest that partial ischemia exists. It was not possible, however, to reproduce a degree of persistent partial ischemia comparable to that in a tourniquet lesion produced directly by occlusion of blood vessels.

As was previously noted, this pressure lesion affects the motor function of the nerve much more than the sensory. Though general physiologic considerations appear to relate this selective effect of ischemia to the size of the nerve fiber, the histologic features of the ischemic lesion give little support to such a hypothesis, for histologic defects are demonstrable in all sizes of fibers concurrently.

It is evident that the intermediate degree of pressure lesion with which we have been concerned is that described by Erb and cited in the introduction of this paper. In this late involvement of painful sensation, its initial instability and its pronounced delay in onset, it appears to be identical with the type of paralysis produced by localized pressure on human nerve by Lewis, Pickering and Rothschild.[1] These investigators did not proceed to the stage of lasting damage to the nerve. The studies of Lewis and Pochin [26] indicated that a tight band at the base of one finger will also induce a much later failure of sensation than will a cuff on the upper portion of the arm. The selective effect on the longest fibers in the limb (centripetal paralysis) noted by Lewis and his collaborators [1] was not investigated, but in any case this type of failure, in which defect in motor conduction was a late event, was observed by these investigators only with compression of wide extent.

The intermediate degree of ischemic lesion is also of theoretic interest in view of the evidence it offers that the structural dependence of peripheral nerve and muscle on central neuronic connection is based on anatomic continuity, and not on streams of impulses.

SUMMARY AND CONCLUSIONS

1. With compression of short segments of peripheral nerve, great variation in rate and extent of impairment of conduction is caused by uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia due to escape of some small vessels.

2. Under such conditions the onset of paralysis is in general more rapid the greater the applied pressure. This relationship is an expression of corresponding relative degrees of ischemia, and not a direct consequence of pressure on nerve fibers.

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26. Lewis, T., and Pochin, E. E.: Effects of Asphyxia and Pressure on the Sensory Nerves of Man, Clin. Sc. **3**:141-155, 1938.

3. If care is taken to avoid angulation, no immediate structural damage is apparent within two hours after application of high pressure and resulting block of conduction.

4. The effect of pressure on conduction may be graded as of four degrees: nil; paralysis with rapid complete recovery on release of pressure; paralysis with delayed recovery without degeneration (intermediate type of pressure lesion), and complete anatomic lesion with degenerative phenomena. Attention is drawn to the third degree, which represents a lesion lasting from one to nineteen days, possibly longer, without signs of loss of excitability below the lesion and with preservation of gross sensation throughout.

5. This intermediate degree of paralysis is associated with early vacuolation and swelling of axis-cylinders and with vacuolation of myelin. After forty-eight hours there is disappearance of myelin, beginning at the nodes of Ranvier. The axis-cylinder loses its argentophil property in this region and becomes thickened in the remaining intervening segment. At a maximal stage of the lesion the demyelinated segment becomes as long as the segment retaining myelin. There is considerable mesodermal reaction. Below the region of compression the demyelinated segments progressively shorten, and normal structure is regained. In some preparations the part of the nerve distal to the site of compression shows beading of myelin and axis-cylinders. The motor end plates and muscle fibers retain their normal appearance. These histologic changes outlast the return of conductivity.

6. There is some evidence that return of conductivity is associated with the appearance of a thin coating of myelin over the previously bared segment.

7. The demyelinated argentophobe region of the axis-cylinder acquires an affinity for iron hematoxylin.

8. Loss of myelin and of the argentophil property of the axon is accompanied by loss of conductivity without loss of the trophic influence of the cell body of the neuron on the distal segment of the axon. There is no adequate explanation for the greater effect of the lesion on conduction of motor impulses.

9. From the evidence presented atrophy of paralyzed muscle appears to be prevented by anatomic connection with the motor neuron in the absence of nerve impulses.

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ATROPHY OF BASAL GANGLIA IN PICK'S DISEASE

A CLINICOPATHOLOGIC STUDY

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Although several observers in recent years have commented on the occurrence of changes in parts of the central nervous system other than the cerebral cortex in the condition of symmetric cortical atrophy first described by Pick, most workers continue to emphasize the cortical changes in their evaluation of the clinical signs and symptoms.

The present case is reported as a good example of the extensive changes which may occur in subcortical gray masses in Pick's disease.

REPORT OF A CASE

R. B., aged 48, a former electrical engineer, was admitted to the Rochester Municipal Hospital, March 17, 1936. He said, "The doctor says I'm nervous, but I feel swell."

Family History.—The family history was without significance.

Personal History.—The patient had been healthy prior to the present illness. He finished college at the age of 18 and up to 1932 had worked successfully as an engineer, to which profession he brought a mathematical talent. He had always been sociable and affable, but reticent, and found his interests mostly with his family.

Present Illness.—The onset was so gradual that it was difficult to state when it occurred. He lost his position in 1932 because of the economic depression and showed a normal amount of concern. He tried to patent an invention, without success, and was keenly discouraged. In 1934, two years before his admission to the hospital and five years before his death, he attempted to sell real estate but failed completely. At this time it was observed that he was unable to organize his work, that he seemed indifferent to his home and family and that he was slow in his behavior. During the six months prior to admission he seemed to age suddenly, his speech became uncertain, he stuttered and his gait took on a "mincing" quality. He showed increasing indifference to his children, became extremely meticulous in his personal habits and dress but at the table was gluttonous. In spite of enormous ingestion of food he continued to lose weight. Whereas he had always been a free spender, he became penurious. His sexual drive was increased. Deterioration in writing was evident in letters he had written to a brother. A letter written in January 1936 was normal in content and form. A letter written one month later consisted of a short but grammatically correct sentence. A letter of March 1936 showed agrammatism: Articles and conjunctions were absent, and the tense and mood of verbs were improperly employed.

Physical Status.—Physical examination revealed nothing remarkable.

Neurologic Status.—Speech was slow and dysarthric; the tongue and hands were tremulous, and the facial expression was rigid, with infrequent blinking of the eyes. Clumsiness in finer movements of the hands and occasionally a cogwheel type of rigidity in the upper extremities were evident. The gait showed a slight tendency toward propulsion.

Psychiatric Status.—He appeared confused and apathetic, and his mental processes seemed much slowed. He was correctly oriented; memory was good for remote events but much impaired for recent events, and attention and calculation were faulty. Insight was lacking, and judgment was poor. He presented a picture of moderately advanced mental deterioration of organic type.

Laboratory Studies.—The blood, urine and spinal fluid were normal.

Course in Hospital.—He remained confused, seclusive and indifferent. His only interest was the radio; he requested certain programs and supposedly read books and newspapers, the

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contents of which he was unable to recall. He was discharged to his home on March 24, 1936 and was examined biannually there.

Subsequent Course of Illness.—He gradually became impulsive and childish in behavior. His scolding of the dog was like that of a 4 year old child. He performed pill-rolling movements with his thumb and forefinger, and sialorrhea became pronounced. In January 1937 he showed bilateral grasp reflexes and increased cogwheel rigidity in all extremities. He read aloud in an agrammatic manner. He could draw a house and a piston, but in writing he frequently misspelled simple words.

Mental deterioration continued, and by March 1938 he was unable to walk. He could make only peculiar clucking or sucking sounds. When an object was placed to his lips, he made sucking movements. Frequently he choked on the food given him. Neurologic

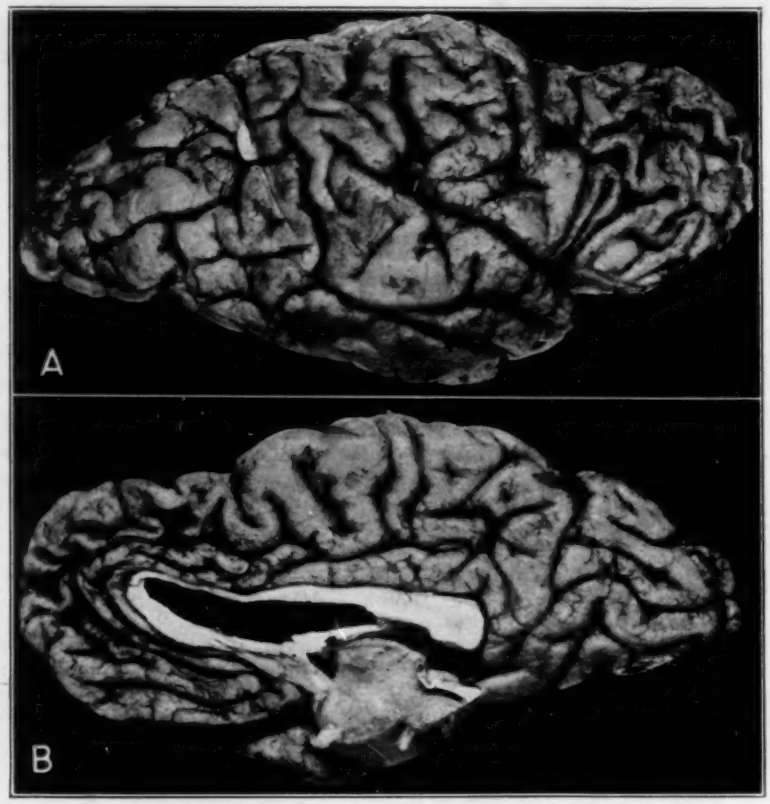

Fig. 1.—*A*, lateral view of right cerebral hemisphere, showing extreme atrophy of the frontal lobe. The process involves area 6 of Brodmann and spares the precentral gyrus and the region posterior to the rolandic fissure. *B*, mesial view of right cerebral hemisphere. The anterior portions of the frontal lobe, including the callosal-marginal (superior frontal) convolution and the anterior half of the cingular gyrus, are atrophied, while the paracentral lobule and the convolutions posterior to it are fairly well preserved. 0.8 natural size.

examination revealed spasticity with cogwheel rigidity, extreme forced innervation in both hands, occasional generalized tremors of the body and profuse salivation. The deep reflexes were hyperactive but equal on the two sides, and the plantar reflexes were normal. He was incontinent of urine and feces. Decubitus ulcers developed; the dysphagia increased, and on Jan. 23, 1939, approximately five years after onset of the disease, he died suddenly.

Gross Pathologic Observations.—Autopsy was performed four hours after death by Dr. Robert Hettig. Pulmonary emboli and bronchopneumonia were the immediate cause of death. Brown atrophy of the heart and mild arteriosclerosis were noted.

The brain weighed 910 Gm. The leptomeninges were edematous, thick and slightly adherent to the atrophied gyri. The atrophy involved the frontal lobes symmetrically, and the demarcation between the atrophied areas and the normal convolutions was sharp (fig. 1 *A*). Mesially, the anterior portions of the frontal lobe, including the callosal-marginal (superior frontal) convolution and the anterior half of the cingular gyrus, were atrophied, and the anterior half of the corpus callosum was notably thinned (fig. 1 *B*). On section, the entire ventricular system was observed to be dilated, especially the anterior horns of the lateral ventricles. The caudate nucleus (head, body and tail) was almost completely destroyed bilaterally, the structures being replaced by a deep brown area of pigmentation (fig. 2 *A*). The ventricular surface was deeply corrugated in this area. The thalamus, subthalamic nucleus and substantia nigra on both sides had a rusty coloration. The globus pallidus was shrunken and deeply pigmented bilaterally. The region of the nucleus of the terminal stria also had a deep brown

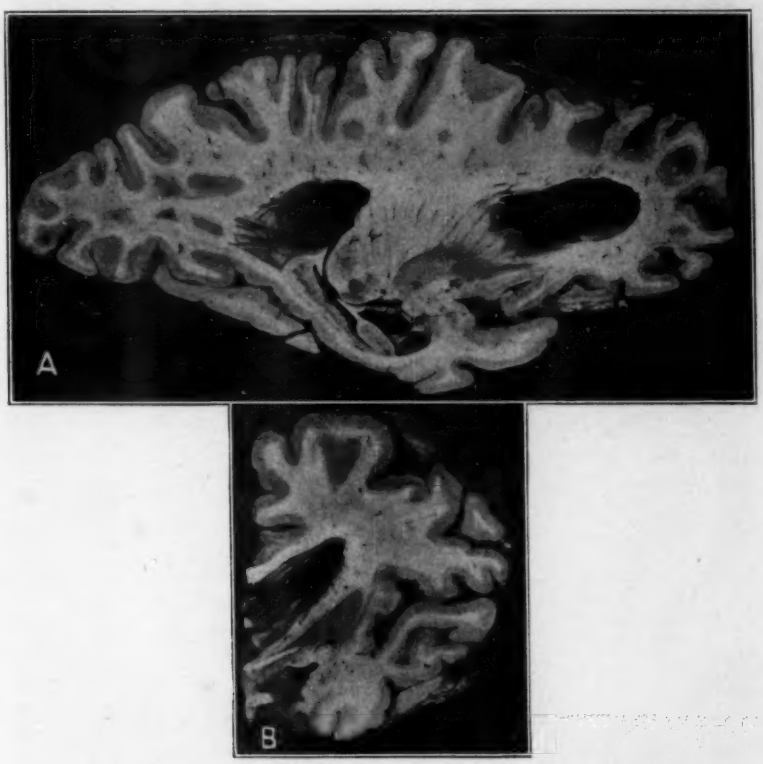

Fig. 2.—*A*, sagittal section of right cerebral hemisphere through the pulvinar, the external geniculate body, the head of the caudate nucleus and the putamen. Note the almost complete destruction of the caudate nucleus and the corrugated ventricular surface in this region. 0.8 natural size. *B*, transverse section of left cerebral hemisphere through the optic chiasm and the anterior commissure. The globus pallidus is much shrunken and has a deep rust color. The head of the caudate nucleus is almost completely destroyed. The region of the nucleus of the terminal stria is deeply pigmented. The putamen and claustrum are well preserved. Natural size.

coloration (fig. 2 *B*). The midbrain and hindbrain were diminished in size. The cerebellum was normal in size and appearance.

Microscopic Examination.—With von Braunmühl's stain no senile plaques were seen. Bielschowsky's silver stain revealed no argentophilic bodies. Many of the neurofibrillae of the diseased nerve cells and their processes were ballooned. This was especially apparent in the most severely involved areas, such as area F E, the subthalamic nucleus and the globus pallidus. Turnbull's stain revealed small amounts of iron pigment in the atrophied cortex of the frontal lobes. In the subcortical nuclear masses, on both sides, enormous quantities

of iron were noted in the globus pallidus and the subthalamic nucleus, and a lesser amount in the substantia nigra (especially the zona reticulata) and the nucleus of the terminal stria. Surprisingly, no iron was seen in the greatly atrophied caudate nucleus. No iron was noted in the putamen, the amygdala, the red nucleus, the cerebellum or the nuclei of the hindbrain. The iron was present in the form of minute granules in the cytoplasm of diseased and normal-appearing nerve cells and in oligodendrocytes and astrocytes and was lying free in the paren-

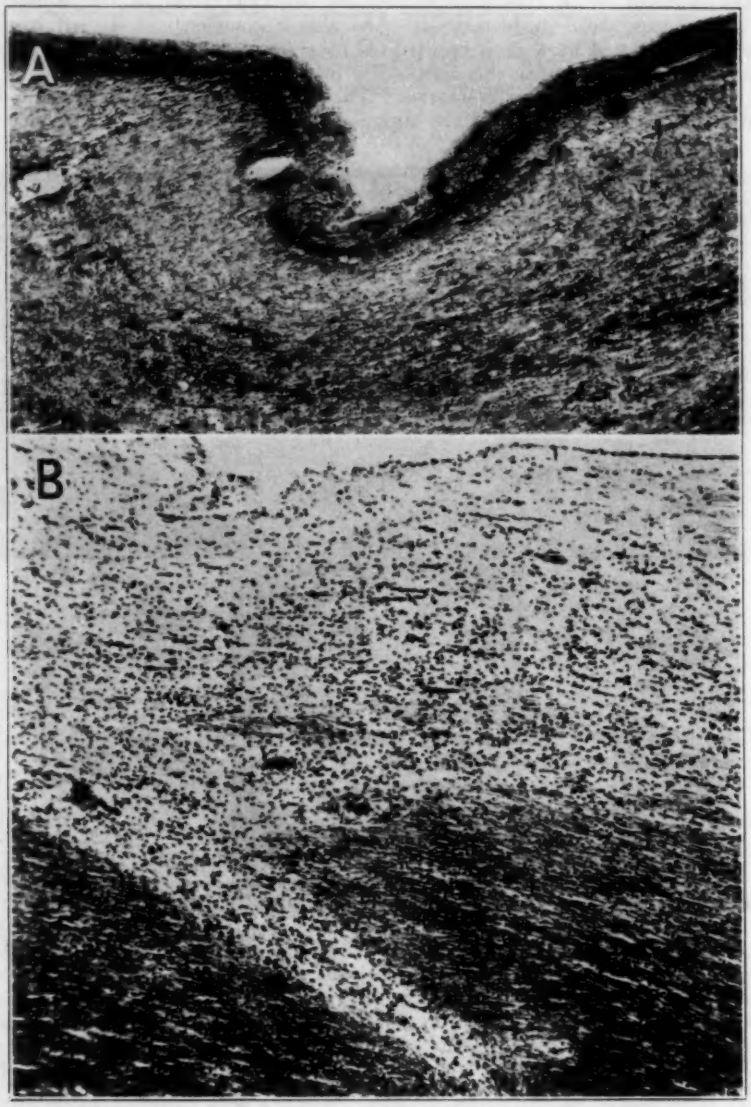

Fig. 3.—*A*, photomicrograph of section from left caudate nucleus, showing excessive subependymal gliosis. The entire caudate nucleus is shrunken and replaced by moderate gliosis. Mallory's phosphotungstic acid hematoxylin stain. *B*, section from the same region as that represented in *A*, showing almost complete disappearance of myelin in the caudate nucleus. The internal capsule is well myelinated. The ependymal lining is not hyperplastic. There is an apparent great increase in the number of glial nuclei throughout the entire caudate nucleus. Smith-Quigley stain; × 100.

chyma. This occurred both in the cortex and in the subcortical nuclear masses already mentioned. In the latter, large clumps of iron were also noted in the neuroglia and lying

free in the parenchyma. No iron was seen in the walls of the blood vessels or in the perivascular spaces.

Stains for fat (scarlet red) showed only occasional globules of neutral fat in the perivascular spaces of the globus pallidus and the subthalamic nucleus. Little fat was seen in the atrophied cortex or the caudate nucleus. Throughout the brain, droplets of orange-staining substances, probably lipochromes, were seen in the cytoplasm of the lipophilic nerve cells. Glial stains (Holzer and the Mallory phosphotungstic acid hematoxylin) disclosed an excessive glial feltwork, with an apparently considerable increase in the number of nuclei throughout the portions of the central nervous system most severely involved (fig. 3*A*).

Myelin stains (Pal-Weigert and Smith-Quigley stains) showed diffuse loss of myelin throughout the white matter of the atrophied cortex, with the U fibers relatively better pre-

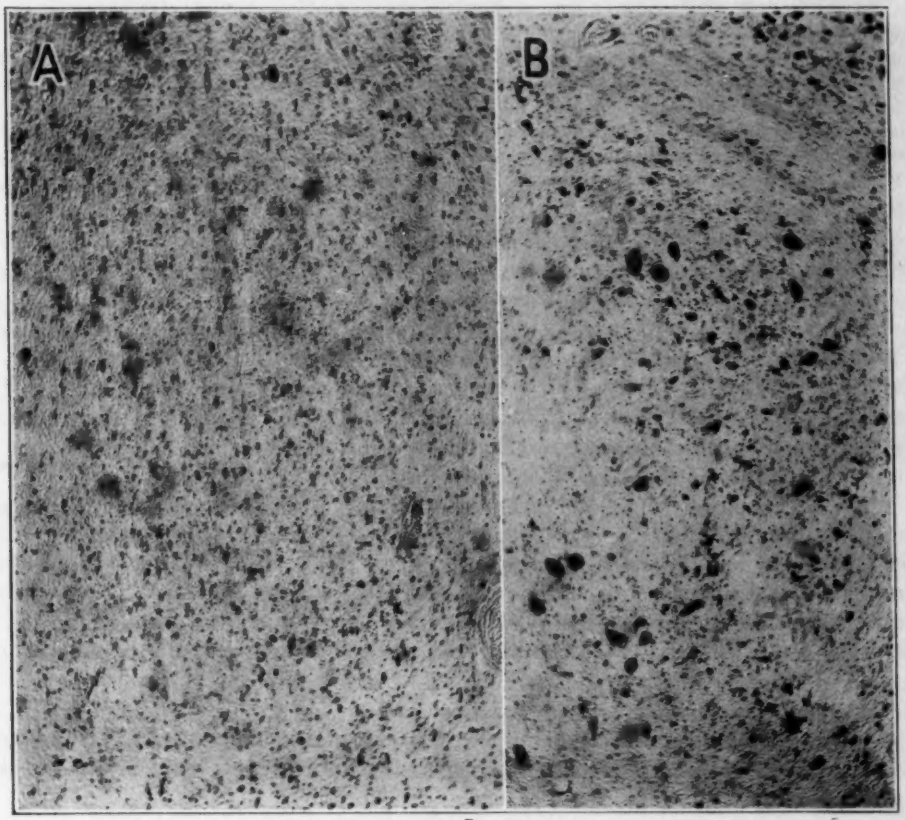

Fig. 4.—*A*, photomicrograph of section from left subthalamic nucleus (corpus Luysi). Only two neurons are visible, and both are swollen and filled with lipochromes. The darkly staining, round bodies observed predominantly in the lower half of the field stain intensely blue with Turnbull's stain. *B*, photomicrograph of section from right substantia nigra. A few normal-appearing, melanin-containing nerve cells are seen. However, the predominant picture is that of masses of melanin lying free in the parenchyma. No melanin was seen in the perivascular spaces. With Turnbull's stain very little iron was seen in this involved area, but iron was moderately abundant in the zona reticulata. Thionine stain; × 100.

served. In the caudate nucleus the myelin was practically destroyed (fig. 3*B*) but was well preserved in the subadjacent internal capsule and in the putamen. In the globus pallidus the internal and, to a less degree, the external medullary laminas were pale. The region of the ansa lenticularis was almost completely devoid of myelinated fibers. The fasciculus lenticularis (field H 2) and the subthalamic fasciculus had fewer fibers than normal. In the cerebral peduncles there was diffuse diminution in myelin, and the frontopontile tract appeared most involved.

Thionine stains of the cerebral cortex revealed that the changes in the atrophic gyri consisted of a notable diminution of cells in all layers, especially in the third layer; cells that remained appeared sclerosed or quite normal. Swollen cells were infrequently seen.

In the subcortical nuclear masses the changes were variable. In the entire caudate complex few nerve cells remained; of these, most were sclerosed, although occasional normal-appearing neurons were seen. In the globus pallidus and the subthalamic nucleus the nerve cells were greatly diminished in number, and the most frequent change consisted of swelling of the cytoplasm, with lipochrome pigments, absence of Nissl granules and displacement of the nucleus to one side (fig. 4 *A*). The large and small nerve cells of the putamen were normal in appearance and number. In the substantia nigra the number of cells was greatly diminished, but the few that remained appeared normal. Large quantities of melanin were seen scattered and lying free in the parenchyma (fig. 4 *B*).

In the red nucleus, the thalamus and the pulvinar, large quantities of lipochromes were observed in the cytoplasm of the nerve cells. Similar deposits were seen in the inferior olives, the pontile nuclei and the nuclei of the cranial nerve. It should be emphasized that in Pal-Weigert stains the lipochromes in these nuclear masses, as well as in the globus pallidus and the subthalamic nucleus, did not stain black, as do the nerve cells in cases of amaurotic family idiocy. The cerebellum revealed diminution in Purkinje cells and hypertrophy of the glia in Bergmann's layer. The blood vessels throughout the brain showed no changes that would not normally be seen in a person of the patient's age.

COMMENT

Clinical Features.—The masked facies, the cogwheel rigidity and a certain amount of propulsion in the gait suggested the possibility of an early parkinsonian syndrome, but the associated profound dementia made this diagnosis untenable. Dementia paralytica was ruled out by laboratory studies. The final diagnosis was Pick's or Alzheimer's disease. In spite of numerous contributions to the differential diagnosis of those two diseases on clinical signs alone, it is quite impossible to make such a diagnosis unless the results of biopsy and encephalographic studies are utilized.

The occurrence of bilateral forced innervation late in the course of the disease suggests that area 6 of the frontal lobe was involved bilaterally (Adie and Critchley [1]; Richter and Hines [2]). However, forced innervation and forced grasping and groping occur frequently in severely demented patients and when present bilaterally have little, if any, localizing value. The presence of the sucking reflex is, I believe, merely the result of the profound retrogression in behavior and had no localizing value in this case at least. Stern,[3] in his study of a patient with severe organic dementia associated with sucking and grasping phenomena, observed at autopsy a unique selective degeneration of the thalamus bilaterally. This sucking reflex, as is the case of bilateral forced grasping and groping, may be merely the manifestation of a profound organic mental deterioration.

Pathologic Features.—The cortical atrophy was typical in nature and distribution of that associated with Pick's disease. However, the changes were not limited to the cortex alone but involved diffusely the entire brain in varying degrees. This is in agreement with the observations of Hassin and Levitin [4] and of Edwards and Swan.[5]

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The atrophy of the caudate nucleus was greater than in any case hitherto reported in the literature. Of all the subcortical gray masses, the caudate nucleus appears to be most frequently involved (Edwards and Swan,[5] Jansen [case 2],[6] Löwenberg [case 4],[7] Onari and Spatz,[8] Ley and associates[9] and von Braunmühl [several collected cases][10]). Other investigators have described changes in other parts of the subcortical gray masses; Gullain and associates[11] reported a case with involvement of the olives and the globus pallidus, and van Bogaert[12] noted lesions in the pallidum and in the region of the corpus Luysi (subthalamic nucleus), which he asserted produced choreoathetosis during life. Giljarowsky[13] and Verhaart[14] observed changes in the cerebellum and pons. It is possible that the case of Stern[3] may be included in this broader concept of Pick's disease.

In view of the extensive changes in the cortex and the subcortical gray masses it is difficult, in fact impossible, to correlate the parkinsonian syndrome and the anatomic changes. The oldest changes in the subcortical gray masses were those in the caudate nucleus; more recent changes occurred in the substantia nigra, and the most recent changes were observed in the globus pallidus and the subthalamic nucleus. This suggests that the lesion in the caudate nucleus was the basis of the cogwheel rigidity, the rigid facies, the tremor and the propulsive gait observed in the patient three years before death. It should be emphasized, however, that Browder and Meyers[15] extirpated the head of the caudate nucleus for relief of postencephalitic tremors with good results. The various hypotheses concerning the anatomic basis of these syndromes of the extrapyramidal tracts, as advanced by Walshe,[16] Jakob[17] and the Vogts,[18] show that to date knowledge of these disorders is extremely meager.

Two types of changes in the nerve cells were seen in this case. In the frontal lobe and the caudate nucleus the cells appeared sclerosed; these regions were probably the first to be affected, and the picture suggests a completed pathologic

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17. Jakob, A.: The Anatomy, Clinical Syndromes and Physiology of the Extrapyramidal System, Arch. Neurol. & Psychiat. **13**:596 (May) 1925.

18. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen der striären Systeme, J. f. Psychol. u. Neurol. **25**:627, 1920.

process. In the globus pallidus and the subthalamic nucleus the diseased nerve cells were swollen and filled with lipochromes; these changes are suggestive of a more acute degenerative process. It is also possible that the presence of iron in large quantities in the globus pallidus and the subthalamic nucleus, in contrast to the small amount in the cortex and its absence in the caudate nucleus, indicates a chronologic difference in the occurrence or the activity of the lesions. The distribution of the iron chiefly in the oligodendrocytes, the astrocytes and the nerve cells indicates that the process was degenerative rather than inflammatory (Metz [19]). The topographic distribution of the iron deposits can be correlated to a slight degree with the results of studies on normal brains by Guizetti, Spatz and others (Hernandez [20]). According to these workers, the globus pallidus (especially the oral portion) and the substantia nigra (especially the zona reticularis) are most abundant in iron, and the striatum and the subthalamic nucleus belong to the second group of iron-containing centers. The cerebral and cerebrellar cortex normally contain much less iron than the structures just mentioned.

Efforts, especially by Onari and Spatz,[8] have been made in the past to explain the elective involvement of the central nervous system in Pick's disease on the basis of Edinger's theory that in all system degenerations which are due to "abiotrophy" the process affects the more recent structures exclusively. No confirmation of this hypothesis is found in this case. The caudate nucleus, belonging to the neostriatum, was almost completely destroyed; the globus pallidus, which is phylogenetically much older, was severely involved, and yet the putamen was fairly well preserved. According to the Vogts,[18] there is practically no difference in structure and origin between the caudate nucleus and the putamen.

It is doubtful whether the changes in the caudate nucleus and the pallidum are a result of retrograde degenerative changes secondary to the cortical involvement. In many cases with severe cortical involvement reported in the literature no changes in the basal ganglia have been present. In monkeys, Mettler [21] observed degenerated fibers to the caudate nucleus, globus pallidus, substantia nigra and subthalamic nucleus after unilateral ablations of area 9, and Hirasawa and Kato [22] noted degenerated corticofugal fibers to the head of the caudate nucleus, putamen, globus pallidus and substantia nigra after cauterization of areas 8 (α, β, γ, δ) and 9 (c, d). However, in man, no evidence has been presented to indicate direct fiber connections between the cortex and the striatum and pallidum (Vogts [18]).

SUMMARY AND CONCLUSION

In a clinicopathologic study of a case of Pick's disease extensive bilateral involvement of the caudate nucleus, the substantia nigra, the pallidum and the subthalamic nucleus was observed.

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19. Metz, A.: Die drei Gliazellarten und der Eisenstoffwechsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:428, 1926.

20. Hernandez, R.: Iron Content of the Brain (Its Normal and Pathological Occurrence), Psychiatric Quart. **5**:95, 1931.

21. Mettler, F. A.: Corticofugal Fiber Connections of the Cortex of Macaca Mulatta: The Frontal Region, J. Comp. Neurol. **61**:509, 1935.

22. Hirasawa, K., and Kato, K.: Ueber die Fasern, insbesondere die corticalen extrapyramidalen aus den Areae 8 (α, β, γ, δ) und 9 (c, d) der Grosshirnrinde beim Affen, Folia anat. japon. **13**:189, 1935.

AGENESIS OF THE CORPUS CALLOSUM WITH POSSIBLE PORENCEPHALY

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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The accumulation of reported data from twenty-five years of pneumoencephalographic studies has directed the interest of neurosurgeons to certain rare anomalous conditions of the brain which may be demonstrated in the encephalogram. These include agenesis of the corpus callosum, porencephalic cysts and cysts of the cavum septi pellucidi and the cavum Vergae. Interesting as these lesions are from a morphologic and a diagnostic standpoint, their study may be especially important because of the possibility that some abnormalities of mental and physical development, hitherto attributed to birth injury, may originate in embryonic or developmental defects of the brain. In this paper are reviewed all the reported cases in the English literature in which an antemortem diagnosis of agenesis of the corpus callosum was made. An additional case associated with a suspected porencephalic cyst is reported. Cysts of the cavum septi pellucidi and the cavum Vergae are discussed under "Differential Diagnosis."

HISTORICAL REVIEW

The first case of agenesis of the corpus callosum was reported by Reil [1] in 1812. In this, and in 81 other cases collected from the literature up to 1933 by Baker and Graves,[2] the condition was encountered incidentally at autopsy, only 2 of these being in the United States. In spite of the facility of ventriculography and encephalography since 1918 (Dandy [3]), not until 1934 did Davidoff and Dyke [4] report the first case of agenesis of the corpus callosum seen in a living patient by encephalography. The encephalogram in the first of 3 cases was interpreted as showing a cyst of the cavum septi pellucidi, and at autopsy, after a craniotomy, complete agenesis of the corpus callosum was noted. Likewise, in the first of 5 cases reviewed by Hyndman and Penfield [5] partial agenesis of the corpus callosum was discovered at operation in a case in which a cyst of the cavum septi pellucidi was suspected.

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* This work was done while Dr. Chaffee was Fellow in Surgery at the Cleveland Clinic.

1. Reil, J.: Mangel des mittleren und freien Theils des Balkens in Menschengehirn, Arch. f. d. ges. Physiol. **11**:341, 1812.

2. Baker, R., and Graves, G.: Partial Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. **29**:1054 (May) 1933.

3. Dandy, W. E.: Ventriculography, Ann. Surg. **68**:5, 1918.

4. Davidoff, L. M., and Dyke, C. G.: Agenesis of the Corpus Callosum: Its Diagnosis by Encephalography; Report of Three Cases, Am. J. Roentgenol. **32**:1 (July) 1934.

5. Hyndman, O. R., and Penfield, W.: Agenesis of the Corpus Callosum: Its Recognition by Ventriculography, Arch. Neurol. & Psychiat. **37**:1251 (June) 1937.

EMBRYOLOGY

In the human fetus the corpus callosum develops between the third and the fifth month (fig. 1). The lamina terminalis connects the bilaterally expanding cerebral hemispheres. Emerging as a thickening of the lamina terminalis are the structures which later bridge the hemispheres, namely, the corpus callosum, the hippocampal commissures of the fornices and the anterior commissure. They grow together dorsally over the thalamus to form eventually a broad decussating band. The portion of the lamina terminalis forming the septum between the corpus callosum and the fornix becomes hollow from stretching and is known as

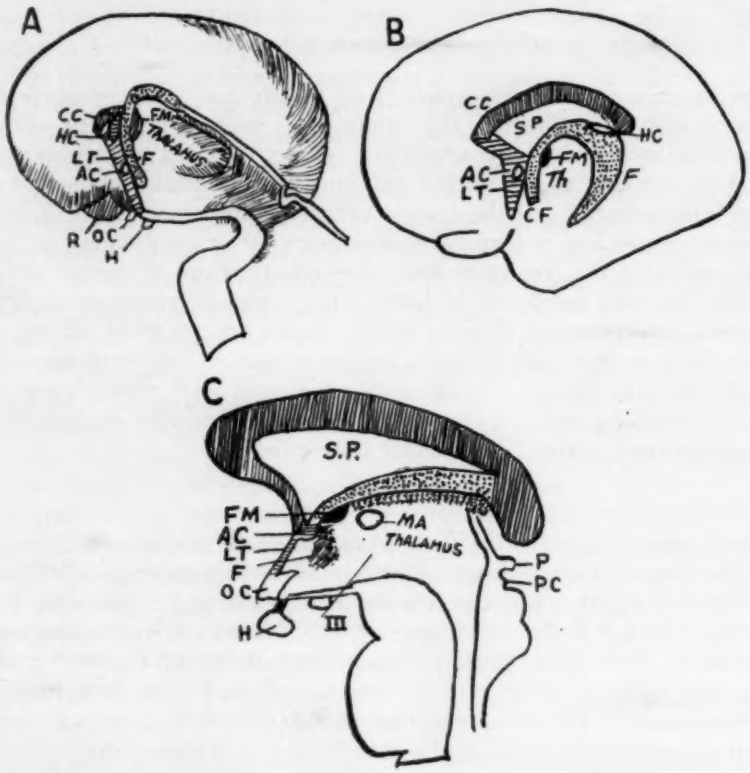

Fig. 1.—Schematic representation of the development of the septum pellucidum and corpus callosum (modified from Ranson [Anatomy of the Nervous System, ed, 6, Philadelphia, W. B. Saunders Company, 1939] and Hyndman and Penfield [5]). *A*, at 3 months of age; *B*, at 5 months of age, and *C*, from an adult.

In this figure, *A. C.*, indicates anterior commissure; *C. C.*, the corpus callosum; *C. F.*, the columna fornices; *F*, fornix; *F. M.*, foramen of Monro; *H*, hypophysis; *H. C.*, hippocampal commissure; *L. T.*, lamina terminalis; *M. A.*, massa intermedia; III, third ventricle; *O. C.*, optic chiasm; *P.*, pineal body; *P. C.*, posterior commissure; *R*, rhinoencephalon; *S. P.*, septum pellucidum, and *Th.*, thalamus.

the cavum septi pellucidi. It lies cephalad to the third ventricle. Any arrested development of the corpus callosum is usually associated with faulty development of contiguous structures. Apparently, the extent depending on the time of embryonic arrest, abnormalities vary from a small defect in the splenium to complete absence of the corpus callosum, septum pellucidum, lyra of the fornices

and anterior commissure. Complete absence of the corpus callosum was noted in over half the cases here reviewed.

In determination of the stage in the embryonic process at which arrested development occurs, Bruce's [6] subdivision is generally recognized.

First three weeks: Complete absence of corpus callosum, when hemispheres and ventricular system are a single, undivided unit.

Four weeks through three months: Absence of corpus callosum and anterior commissure, but perfect division of cerebral hemispheres by longitudinal fissure.

During fourth month: Absence of corpus callosum; presence of anterior commissure.

End of fourth month: Presence of anterior commissure and genu of corpus callosum.

Lesser degrees of agenesis of the corpus callosum vary directly in proportion to the lateness of onset of arrested development.

ASSOCIATED ANOMALIES

On the basis of a modification of the list of Baker and Graves,[2] with additions by other authors, the following anomalies frequently associated with agenesis of the corpus callosum are presented:

1. Dilatation of the posterior horns of the lateral ventricles.

2. Failure of the calcarine and parieto-occipital fissure to join because of interposition of a superficial gyrus.

3. Absence of radial arrangement of the sulci on the medial aspect of the hemispheres. This development is similar to that of the brain of a fetus at 6 months.

4. Absence of the septum pellucidum and the hippocampal commissure associated with total agenesis of the corpus callosum. The septum pellucidum is present in cases of partial agenesis of the corpus callosum.

5. Association of absence of the corpus callosum with at least one other anomaly of the brain: (*a*) cranial nerve defects; (*b*) incomplete separation of the frontal lobes; (*c*) hydrocephalus; (*d*) enlarged anterior commissure; (*e*) porencephaly, and (*f*) arhinencephaly.

6. Rarity of associated bodily defects, including: (*a*) cleft palate; (*b*) harelip; (*c*) cryptorchism; (*d*) thoracic stomach, and (*e*) coloboma of optic nerve.

FUNCTION OF THE CORPUS CALLOSUM

Clinical histories of patients with agenesis of the corpus callosum are interesting in view of the extensive study which has been devoted to the function of the corpus callosum. Cameron [7] claimed that defects other than those of the corpus callosum are responsible for the clinical manifestations of patients with agenesis of the corpus callosum. Tilney [8] pointed out that the opossum does not possess a corpus callosum but apparently has a compensatory hypertrophy of the hippocampal structure. In a strain of house mice King and Keeler [9] observed agenesis of the corpus callosum,

6. Bruce, A.: On the Absence of the Corpus Callosum in the Human Brain with Description of a New Case, Brain **12**:171, 1890.

7. Cameron, J. L.: The Corpus Callosum: A Morphological and Clinical Study, Canad. M. A. J. **7**:609, 1917.

8. Tilney, F.: The Hippocampus and Its Relationship to the Corpus Callosum, J. Nerv. & Ment. Dis. **89**:433 (April) 1939.

9. King, L. S., and Keeler, C. E.: Absence of Corpus Callosum: A Hereditary Brain Anomaly of the House Mouse, Proc. Nat. Acad. Sc. **18**:525, 1932.

which was familial and was inherited as a unit character. Superficial examination of these mice with either partial or complete agenesis of the corpus callosum disclosed no distinguishing abnormalities. Spitzka [10] expressed the belief that a direct relation existed between the thickness of the corpus callosum and mental efficiency. Later Ashby and Stewart,[11] in a study of the brains of mentally defective persons and normal healthy adults, found no correlation between the size of the corpus callosum and the degree of intelligence. Although Alpers and Grant [12] described a clinical syndrome associated with tumor of the corpus callosum, Armitage and Meagher [13] stressed that such deductions are misleading because associated structures of the brain are invariably involved by such infiltrating lesions. Armitage and Meagher,[13] Cameron [7] and Dandy,[14] working independently, by either surgical section of the corpus callosum or clinical evaluation could attribute no function to the corpus callosum. Dandy noted no unusual results from dividing the corpus callosum along the entire anteroposterior extent. Pavlov,[15] however, demonstrated that afferent fibers gave off conditioned reflex fibers to the opposite hemisphere via the corpus callosum. With present knowledge we may conclude that except for the abolition of some conditioned reflex impulses, Bruce's [6] statement seems correct, namely, "that if the brain is otherwise well developed, absence of the corpus callosum does not necessarily produce any disturbance of motility, coordination, general or specific sensibility, reflexes, speech or intelligence."

ETIOLOGIC FACTORS

The causation of agenesis of the corpus callosum has never been conclusively determined. Chemical toxins, syphilis and virus and pyogenic infections have been incriminated, but proof is lacking. De Lange [16] and Cameron [7] differed in their opinions as to whether hydrocephalus is the cause or the result of agenesis of the corpus callosum. According to Cameron, hydrocephalus is more apparent than real, inasmuch as the corpus callosum normally forms the roof of the lateral ventricles. Whatever the causative factor, there has obviously been some degree of arrested development of the corpus callosum in every case.

CLINICAL MANIFESTATIONS

In table 1 are detailed the important clinical observations in the 15 reported cases of agenesis of the corpus callosum diagnosed during the life of the patient by pneumoencephalography. The youngest patient was 6 months old, and the oldest patient, who is the subject of the present paper, was 39 years of age. The age incidence in cases in which autopsy was performed varied from birth to 73 years,

10. Spitzka, E. A.: A Study of the Brains of Six Eminent Scientists, Tr. Am. Philos. Soc. **21**:175, 1907.

11. Ashby, W. R., and Stewart, R. M.: Brain of Mental Defective: Study of Morphology in Its Relation to Intelligence; Corpus Callosum in Its Relation to Intelligence, J. Neurol. & Psychopath. **14**:217, 1934.

12. Alpers, B. J., and Grant, F. C.: The Clinical Syndrome of the Corpus Callosum, Arch. Neurol. & Psychiat. **25**:67 (Jan.) 1931.

13. Armitage, G., and Meagher, R.: Gliomas of the Corpus Callosum, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:454, 1933.

14. Dandy, W. E.: Operative Experience in Cases of Pineal Tumor, Arch. Surg. **33**:19 (July) 1936.

15. Pavlov, I.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G. Anrep, London, Oxford University Press, 1927.

16. de Lange, C.: On Brains with Total and Partial Lack of the Corpus Callosum and on the Nature of the Longitudinal Callosal Bundle, J. Nerv. & Ment. Dis. **62**:449, 1925.

the anomaly in most instances having been noted in persons under 10 years of age. Apparently, sex was not a determinate factor (table 1). Feeblemindedness and convulsive seizures of varying degrees of severity were the most common symptoms of agenesis of the corpus callosum. Other, less constant, symptoms included spastic paraplegia, hyperreflexia, athetoid movements, the Babinski sign, strabismus and nystagmoid movements of the eyes. The spinal fluid pressure might or might not be elevated. There was no history of convulsions in 5 cases, and intelligence was apparently normal in 4 cases. Congenital or developmental physical anomalies were commonly associated with agenesis of the corpus callosum.

ROENTGENOGRAPHIC DIAGNOSIS

The criteria for the encephalographic diagnosis of agenesis of the corpus callosum, as originally established by Davidoff and Dyke,[4] are as follows: (1) marked separation of the lateral ventricles; (2) angular dorsal margins of the lateral ventricles (this corresponds to the bicornuate appearance mentioned by Hyndman and Penfield [5]); (3) concave mesial borders of the lateral ventricles; (4) dilatation of the caudal portions of the lateral ventricles; (5) elongation of the interventricular foramens; (6) dorsal extension and dilatation of the third ventricle, and (7) radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and extension of these sulci through the zone usually occupied by the corpus callosum.

Diagrammatic representations of the results of air studies of the ventricles of the brain in reported cases of agenesis of the corpus callosum have been drawn to scale and are shown together in figure 2. One is particularly impressed with the variations in the size and shape of the lateral ventricles. The pointed dorsal margins of the lateral ventricles, giving an appearance often referred to as bicornuate, are not consistently present. Incomplete filling of the ventricles with air causes distortions (case 3). A cursory inspection of figure 2 shows obvious deviations from normal in all these cases, and for the most part these variations are similar. These pneumoencephalographic standards for the diagnosis of agenesis of the corpus callosum, as originated by Davidoff and Dyke,[4] have served as the pattern for subsequent diagnoses. No other cerebral lesion may be confused with this defect except, possibly, a communicating cyst of the cavum septi pellucidi.

PORENCEPHALY

The case reported here is one of agenesis of the corpus callosum with the possible association of porencephaly. This combination is indeed rare. Inasmuch as proof of the diagnosis is wanting, the evidence without a didactic discussion of the subject is presented. Reeves,[17] in 1939, reported the first case of porencephaly associated with agenesis of the corpus callosum diagnosed in a living patient by encephalographic means. The anomaly in the cases presented by Hyndman and Penfield [5] (case 4, table 2) may have been porencephaly in association with agenesis of the corpus callosum, although the specific diagnosis was not mentioned. At autopsy LeCount and Semerak [18] observed porencephaly in 2 of 4 brains with agenesis of the corpus callosum. These authors defined porencephaly as a defect in the cerebral or the cerebellar structure appearing as a cystlike communication

17. Reeves, D. L.: Congenital Defects of the Cranial Nerves: Associated Porencephaly and Agenesis of the Corpus Callosum Diagnosed by Ventriculography, Bull. Los Angeles Neurol. Soc. **4**:184, 1939.

18. LeCount, E. R., and Semerak, C. B.: Porencephaly, Arch. Neurol. & Psychiat. **14**:365 (Sept.) 1925.

TABLE 1.—*Summary of Clinical Aspects of Patients with Agenesis of the Corpus Callosum Diagnosed During Life*

Author	Case No. and Patient's Initials	Age and Sex	Type of Agenesis	History and Physical Findings	Intelligence	Congenital or Developmental Defects	Subsequent History
Davidoff and Dyke [4]	1 N. E.	6 yr. F	Complete	Left-sided jacksonian convulsions, beginning at 3 years of age; left hemiparesis; sudden onset of latter at age of 2 years, with unconsciousness, vomiting and fever of 2 weeks' duration	High	Hypoplasia of left side of body; premature puberty	Diagnosis of cyst of cavum septi pellucidi by encephalogram. Craniotomy revealed cyst with colorless fluid. Patient died after operation. Complete agenesis of corpus callosum seen at autopsy
	2 E. R.	21 yr. M	Partial	Frontal headache once a month since age of 14 years; grand mal seizures, mostly on left side; ataxia in left arm; partial defect in left superior homonymous quadrant of visual field	.....	.....	Diagnosis of agenesis of corpus callosum; no operation
	3 M. S.	3 yr. F	.....	Premature birth; grand mal convulsions, tending to start on right side; onset at age of 2 years, 4 months; no abnormal neurologic signs	Retarded	Physical retardation	Craniotomy after diagnosis of cyst of cavum septi pellucidi. Patient survived operation
Hyndman and Penfield [5]	4 N. M.	8 yr. F	Partial	Born after 48 hours' labor, forceps delivery; left handed; difficulty in sentence formation; right jacksonian convulsions since 4 years of age; nystagmus upward and to left; slight internal squint of right eye; deviation of tongue to right; intention tremor in right hand; spinal fluid pressure 420 mm. water (sitting position)	Normal	None	Original diagnosis was cyst of cavum septi pellucidi. Craniotomy performed; no defect seen. Diagnosis made after experience with subsequent cases
	5 S. V.	18 mo. F	Partial	Normal birth; petit mal attacks since 6 months of age; no localizing signs; voluntary motion slow and athetoid; spinal fluid pressure normal	Retarded	High arched palate	Craniotomy revealed thin pia-arachnoid instead of corpus collosum and enlargement of lateral ventricles
	6 G. D.	21 yr. M	Partial	Forceps delivery at full term; normal childhood; patient failed in history and English, passed in science; patellar reflex greater on right than on left; right hemiparesis	Average	Extremities on left side better developed than those on right	Patient living when last reported on
	7 H. D.	2 yr. M	Complete	Normal birth at full term; no convulsions. Ventricular system displaced by 130 cc. of air	Retarded	Occiput flat; bossed frontal bones	.....

	8 S. S.	5 yr. F	Partial	Normal delivery; petit mal attacks; no convulsions	Normal	None	.....
Cass and Reeves [19]	9 M. F.	9 mo. M	.....	Normal delivery; nystagmus on upward and lateral gaze; patient refused to sit up; no interest in surroundings; no convulsions	Retarded	Flat occiput; bossed frontal bones	Authors believe this condition cannot be distinguished from communicating cyst of cavum septi pellucidi
Reeves [17]	10 J. M.	6 mo. F	.....	Convulsive seizures from 2 months of age; bilateral Babinski sign; blurred optic disks; spinal fluid pressure 375 mm. of water	Retarded	Coloboma of left optic nerve and pigmentary choroidal degeneration	Youngest patient on record in whom agenesis was diagnosed by air studies. Porencephaly associated with agenesis of corpus callosum
Kunicki and Chorobski [31]	11 R. M.	21 mo. M	Complete	Ataxic, aimless movements; bilateral Babinski sign; optic nerve atrophy; no convulsions	Retarded	Unilateral cryptorchism; hydrocephalic skull	Craniotomy revealed complete agenesis; death 9 hours after operation
Gowan and Master	12	19 mo.	.....	Normal delivery; left jacksonian convulsion; left hyperreflexia; head measured 46 cm. at 24 months; left Babinski sign	Retarded	Occiput flat; eyes widely separated	.....
Goldensohn and others [33]	13 M. M.	11 yr. F	Partial	Normal delivery; generalized convulsions, both grand and petit mal; headaches; vertigo; temper tantrums; sexual precocity; enuresis; defective associated swing of left arm; dysdiadokokinesis on left; knee jerk increased on right; Babinski sign and internal strabismus on right; negative visual fields and fundi	I. Q. 80	.....	Electroencephalogram revealed asynchronism of electrical activity between left and right hemispheres, particularly between occipital lobes; waves generally slow
Derbyshire and Evans [32]	14 M. T.	6 yr. F	Partial	Normal delivery; generalized convulsions 3 months previous to admission; general hyperreflexia, hypertonicity and spasticity	Retarded	Bilateral clubfeet	Electroencephalogram revealed fairly good synchronization between left and right hemispheres except between two occipital lobes with patient's eyes open
Bunts and Chaffee	15 C. H.	39 yr. M	Complete	Normal delivery; grand and petit mal seizures since age of 5 months; temporary forgetfulness for recent events; neurologic signs negative except for early edema of optic disk and concentric contraction for color and form in both visual fields, most marked on right; spinal fluid pressure 515 mm. of water with patient in sitting position; 192 cc. of spinal fluid removed	Normal	None	Possible associated porencephalic cyst. Intensity of convulsions diminished for 3 months after encephalographic study; electroencephalogram showed diffuse dysrhythmia, irregular slow waves, absence of normal alpha activity and synchronization between hemispheres except in the occipital regions when the patient's eyes were open

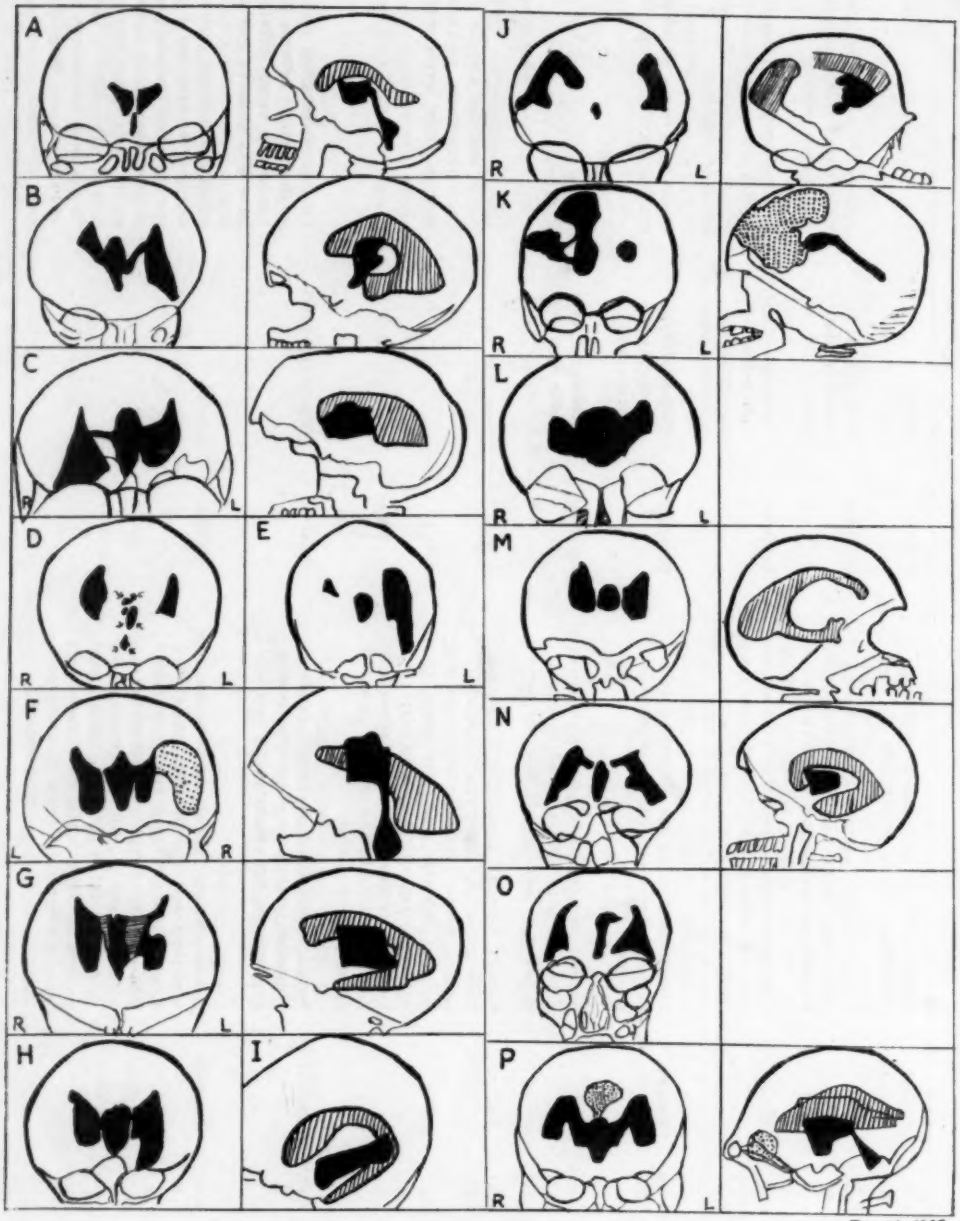

Figure 2

(See legend on opposite page)

with the ventricles, or separated from them by only a thin layer of brain tissue, covered on the outside by the pia-arachnoid and filled with a clear, colorless fluid. A case of porencephaly is diagrammatically illustrated in figure 3 *B*.

DIFFERENTIAL DIAGNOSIS

In the first cases of agenesis of the corpus callosum reported by Davidoff and Dyke [4] and Hyndman and Penfield [5] the condition was diagnosed as cyst of the

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EXPLANATION OF FIGURE 2

Diagrammatic representation of cerebral air studies in reported cases of agenesis of the corpus callosum.

A, normal encephalogram.

B, (Davidoff and Dyke,[4] case 1), widely separated and dilated lateral ventricles, particularly the temporal horns and the posterior portions of the bodies. The third ventricle is high and dilated. The foramen of Monro is elongated.

C (Davidoff and Dyke,[4] case 2), widely separated and dilated lateral ventricles, particularly the posterior portions. The third ventricle is dilated and extends high. The foramen of Monro is elongated.

D (Davidoff and Dyke,[4] case 3), wide separation of the lateral ventricles. Arrows indicate the outline of the third ventricle, which is incompletely filled.

E (Hyndman and Penfield,[5] case 6), wide separation of the lateral ventricles; only partial filling of one ventricle; third ventricle high and dilated.

F (Hyndman and Penfield,[5] case 4), partial agenesis. Wide separation and dilatation of the lateral ventricles, particularly the posterior portions. The third ventricle rises high in the middle of the corpus callosum. Note the appearance of a possible porencephalic cyst associated with the right lateral ventricle.

G (Hyndman and Penfield,[5] case 5), partial agenesis. Dilatation and separation of the lateral ventricles; high extension of the third ventricle; indentation of the falx cerebri. Horizontal stippling indicates broadening of the third ventricle anterior to the optic thalamus.

H (Hyndman and Penfield,[5] case 7), complete agenesis. Dilatation and widening of the lateral ventricles; indentation of the falx on the cephalic aspect of the dilated third ventricle.

I (Hyndman and Penfield,[5] case 8), partial agenesis in the splenium. No evidence of agenesis anteriorly, in the anteroposterior roentgenogram.

J (Cass and Reeves,[19] case 9). The third ventricle is poorly shown in the anteroposterior view. In the right lateral view the third ventricle has a "cocked hat" appearance. Complete filling of the lateral ventricles not seen, although dilatation is present.

K (Reeves,[17] case 10), midline porencephalic cyst with agenesis of the corpus callosum. The right lateral view shows the cyst connected with the lateral ventricle. The author was undecided whether the cyst was connected with the third ventricle.

L (Kunicki and Chorobski,[31] case 11), complete agenesis; anteroposterior view only. The third ventricle is very wide, with consequent wide separation of the lateral ventricles and rises higher than the upper level of one lateral ventricle.

M (Gowan, L. R., and Masten, M. G.: Agenesis of the Corpus Callosum: Diagnosis of a Case by Encephalography, Am. J. Dis. Child. **60**:1381 [Dec.] 1940; case 12), widely separated and dilated lateral ventricles, particularly the posterior portions, and pointed dorsal surfaces of the lateral ventricles. The third ventricle is not visualized in lateral view.

N (Goldensohn and others,[33] case 13), bicornuate, "bat wing" appearance of the lateral ventricles; elongation of the foramen of Monro; dilated, high third ventricle.

O (Derbyshire and Evans,[32] case 14), wide separation and dilatation of the lateral ventricles, with bicornuate appearance. The third ventricle is irregular and extends high between the lateral ventricles.

P (present case; case 15), widely separated and dilated lateral ventricles, with "bat wing" appearance; third ventricle dilated and high, its dome extending above the foramens of Monro The dotted area outlines a possible associated porencephalic cyst.

TABLE 2.—*Encephalographic Evidence of Agenesis of Corpus Callosum*

Case	Lateral Ventricles			Foramen of Monro	Third Ventricle		
	Position	Shape	Size		Position	Shape	Size
1	Separated widely	Concave mesially; dorsal margins pointed	Posterior portion of bodies and temporal horns greatly enlarged; right frontal horn absent; left frontal horn rudimentary	Elongated; widened	Slightly to right of midline; between the lateral ventricles; top located 1.3 cm. dorsal to foramens of Monro	Somewhat triangular in anteroposterior view with base turned dorsally; "cocked hat" appearance from side	Enlarged; 1.9 cm. wide; 4.5 cm. high
2	Separated 4.3 cm.	Concave mesially; dorsal margins pointed	Frontal horns absent; posterior portions of bodies greatly dilated; temporal horns moderately dilated	Elongated; widened	Between lateral ventricles; separated from each lateral ventricle by 1 cm.; top 1.9 cm. dorsal to foramens of Monro	"Cocked hat" appearance from side	1.7 cm. wide; 4.7 cm. high; 5 cm. long
3	Separated 5 cm.	Concave mesially; dorsal margins pointed	Frontal horns narrow; posterior portions of bodies moderately dilated; temporal horns slightly dilated	Not seen	Between lateral ventricles; separated from the lateral ventricles by 1 cm. on left and 0.5 cm. on right	Incomplete filling with air gives appearance of isolated islands of air	1 cm. wide; 3.6 cm. high
4	Separated widely	Bicornuate or angular dorsal surfaces	Enlargement of posterior horns; cystic enlargement of body of left lateral ventricle, with appearance of porencephalic cyst	Elongated; widened	Central; between and almost as high as top of lateral ventricles	Angular cephalic end, rounded base; connection with cerebral aqueduct and fourth ventricle seen in lateral view	About six times normal size
5	Separated widely	Bicornuate	Enlargement of posterior horns	Elongated; widened	Central	Moniliform in anteroposterior view; superior aspect indented by falx cerebri; superior margin horizontal in lateral view	About four times normal size
6	Separated widely	Convexity of mesial borders	Left ventricle larger than right, left indicating atrophy of hemisphere; enlargement of posterior horns	Not seen	Central and high	Wide with rounded apex	About three times normal size
7	Wide	Symmetric; bicornuate	Posterior horns greatly enlarged	Not seen	Central; several centimeters higher than normal	Ovoid; impression of falx on superior surface	About six times normal size

8	Defect in splenium not seen in postero-anterior view	Symmetric; bicornuate	Slightly enlarged	.....	Central; posterior portion above and posterior to upper end of cerebral aqueduct; agenesis in splenium of corpus collosum	Posterior part like tail	Normal anteriorly; wider posteriorly
9	Separated widely	Anterior horns normal; concave mesial margin of right ventricle; lacks bicornuate appearance	Hydrocephalus, involving especially posterior horns	Not seen	Central and high	"Cocked hat" appearance on lateral view	3.5 by 0.6 cm.
10	Separated widely	Indistinct; blended with porencephalic cyst on right	Not enlarged except as right ventricle blends with cyst	Not seen	Central and high; appears to continue into porencephalic cyst	Normal	Author undecided whether continuous with porencephalic cyst
11	Separated widely	Elongated; upper poles inclined outward; rounded dorsal surfaces	Enlarged	Not seen	Central; high as top of lateral ventricle	Domelike roof	Tremendous width
12	Separated widely	Concave mesial borders; pointed dorsal surfaces	Two and a half times normal	Not seen	Central and high	Moniliform; not visualized in lateral view	2.3 by 1.3 cm. in anteroposterior view
13	Wide separation of posterior horns	Bicornuate; "bat wing" appearance	Dilated posterior horns	Elongated; widened	Central and high	Moniliform in antero-posterior view	Dilated
14	Wide separation of posterior horns	Bicornuate; pointed dorsal surfaces	Dilated	Not seen	Central and high; no lateral view submitted	Irregular; vertical; elongated	Elongated about five times normal size
15	Wide separation, particularly of posterior horns	"Bat wing" appearance; rounded cephalad; concave mesial borders	Greatly dilated body and posterior horns	Elongated; widened	Central and high; top rises above foramen of Monro	Moniliform; "cocked hat" appearance in lateral view	3 by 2 cm.

cavum septi pellucidi. Recently Cass and Reeves [19] (case 9) stated that in their case the lesion could not surely be differentiated from cyst of the cavum septi pellucidi. A careful analysis of the pathologic anatomy applied to encephalographic interpretation in most instances will establish a differential diagnosis of agenesis of the corpus callosum and cyst of the cavum septi pellucidi (fifth ventricle) and of the cavum Vergae (sixth ventricle). A cavity within the septum pellucidum occurs much more commonly than is generally appreciated and is seen in almost all infants. Van Wagenen and Aird [20] reported that of 30 consecutive brains examined at the University of Rochester School of Medicine, 18, or 60 per cent, had some dilatation of the cavity of the septum pellucidum.

The cavum septi pellucidi and the cavum Vergae normally are not in communication with the ventricular system, are not lined by ependymal cells and do not contain tela choroidea. Conjectures as to why they happen to contain fluid have been best discussed by Van Wagenen and Aird [20] and by Wolf and Bamford.[21] The cavum Vergae is really the posterior extension of the cavum septi pellucidi.

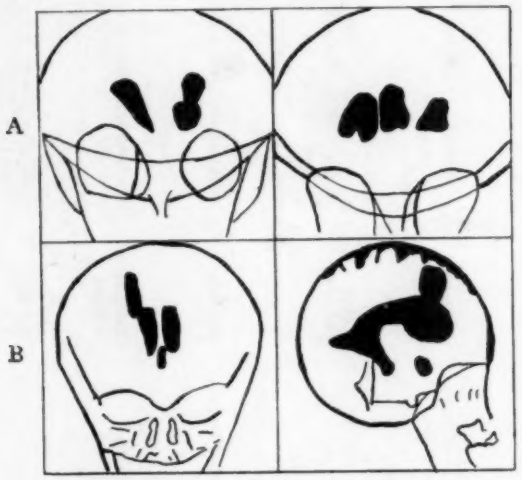

Fig. 3.—Diagrams representing the two conditions which must be differentiated from agenesis of the corpus callosum.

Above, on the left is the ventriculogram of a noncommunicating cyst of the cavum septi pellucidum before rupture, showing dilatation of the lateral ventricles and absence of a central air shadow between them. On the right the central air shadow appears after artificial communication was setablished between the cyst and the ventricle. (From Dandy,[22] page 58; a boy aged 4½ years.)

Below, an anteroposterior and a lateral view of a porencephalic cyst in communication with the right lateral ventricle. The ventricles are slightly dilated but not separated, and the third ventricle is in normal position. (From Reavis, C. W., and Kilby, W. L.: Porencephaly, Bull. School Med. Univ. Maryland **26**:190 [Jan.] 1942; a girl aged 14 months.)

and although the two cavities may be separated by the pillars of the fornix, when dilated they usually communicate with each other through a small defect in the

19. Cass, A. B., and Reeves, D. L.: Partial Agenesis of the Corpus Callosum: Diagnosis by Ventriculographic Examination, Arch. Surg. **39**:667 (Oct.) 1939.

20. Van Wagenen, W. P., and Aird, R. B.: Dilatations of the Cavity of the Septum Pellucidum and Cavum Vergae, Am. J. Cancer **20**:539, 1934.

21. Wolf, A., and Bamford, T. E.: Cavum Septi Pellucidi and Cavum Vergae, Bull. Neurol. Inst. New York **4**:294, 1935.

fornix (fig. 4). The two cavities are bounded anteriorly, superiorly and posteriorly by the corpus callosum, laterally by the walls of the septum pellucidum and inferiorly by the rostrum of the corpus callosum and the lamina rostralis (fig. 4). The cavum septi pellucidi and the cavum Vergae are superior to the third ventricle, being on the same level with, and forming the mesial walls of, the lateral ventricles (fig. 4 *C*). A considerable portion of the septum pellucidum lies anterior to the third ventricle. Therefore the third ventricle is normally inferior to the cavum septi pellucidi and the cavum Vergae, being separated from them by the body of the fornix with its underlying tela choroidea. Furthermore, the third ventricle is beneath the level of the bodies of the lateral ventricles.

Dandy,[22] citing Verga, pointed out cysts of the cavum septi pellucidi and cavum Vergae, and Van Wagenen and Aird[20] classified them as follows: (1) Noncommunicating cyst, which is a closed intact cavity (fig. 3 *A*, on left); (2) communicating cyst, in which a communication with the third or the lateral ventricles has been established as a result of rupture of the walls due to differences in fluid pressure between the cyst and a ventricle (appearance similar to that in figure 3 *A*, on right), and (3) secondary or acquired cyst, in which communicating dilatations are present as a part of later developing, or superimposed, hydrocephalus.

The literature as far back as Verga contains many reports on specimens of cysts of the cavum septi pellucidi and the cavum Vergae. The reports of Dandy,[22] Van Wagenen and Aird,[20] Berkwitz,[23] Leslie[24] and Turnbull,[25] constituting a reasonable search of the English literature, revealed only 16 cases in which the pneumoencephalographic diagnosis of cyst of the cavum septi pellucidi or the cavum Vergae was made. In 5 of these cases the cyst was of the air-containing, communicating type and was diagnosed as such in conjunction with some other pathologic lesion in the brain, such as tumor or arachnoiditis, which accounted for the symptoms of the patient. In 11 cases the cyst was noncommunicating and therefore did not contain air on encephalographic examination, and in each instance the cyst was the only lesion to account for the symptoms. In 10 of these 11 cases of noncommunicating cyst of the cavum septi pellucidi or cavum Vergae, cure was effected when a communication between the cyst and the lateral ventricle was established, by operation, as in the cases of Dandy,[22] Van Wagenen and Aird,[20] Leslie,[24] Tönnis[26] and Kötter,[27] by spontaneous rupture of the cyst wall coincident with changes in pressure during the encephalographic procedure, as reported by Van Wagenen and Aird,[20] Berkwitz,[23] Turnbull[25] and Stookey,[28] or by aspiration of the cyst, as mentioned by Spurling and Jelsma.[29] Evidence of a sudden transition from a symptom-producing, noncommunicating cyst to a symptomless, communicating cyst as a result of spontaneous rupture of the cyst wall is given in the case reported by Van Wagenen and Aird[20] and by Laubenthal.[30]

22. Dandy, W.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle), Arch. Neurol. & Psychiat. **25**:44 (Jan.) 1931.

23. Berkwitz, N. J.: Noncommunicating Cyst of the Septum Pellucidum, Minnesota Med. **22**:402, 1939.

24. Leslie, W.: Cyst of the Cavum Vergae, Canad. M. A. J. **43**:433, 1940.

25. Turnbull, F.: Cyst of the Septum Pellucidum and Epilepsy, Bull. Vancouver M. A. **15**:183, 1939.

26. Tönnis, W.: Kongenitale Cyste des Septum pellucidum, Zentralbl. f. Chir. **62**:1018, 1935.

27. Kötter, E.: Ueber das Cavum septi pellucidi und andere Veränderungen des Septum Pellucidum, Nervenarzt **9**:392, 1936; cited by Laubenthal.[30]

28. Stookey, cited by Van Wagenen and Aird.[20]

29. Spurling, R. G., and Jelsma, F., cited by Van Wagenen and Aird.[20]

30. Laubenthal, F.: Ueber Veränderungen des Septum pellucidum, Nervenarzt **10**:401, 1937.

Many postmortem specimens exist in which the communicating type of cyst of the cavum septi pellucidi and cavum Vergae was present without symptoms or in conjunction with other lesions to account for the symptoms. Although there are available even a greater number of specimens of small, noncommunicating cysts

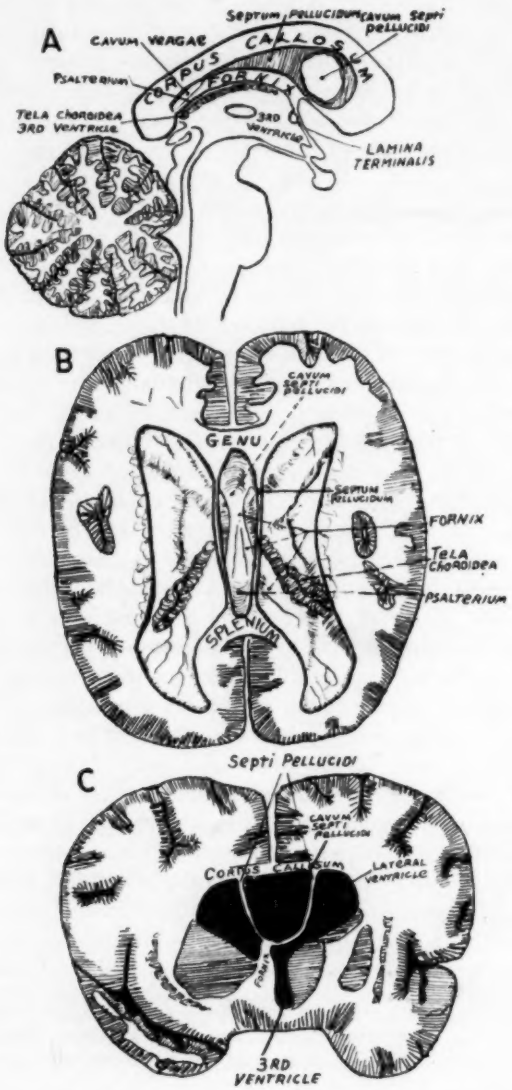

Fig. 4.—*A*, sagittal view, showing small cavum Vergae separated from the cavum septi pellucidi by a slender partition of fornix. (Diagram after Dandy,[22] page 48.)

B, large cavity formed by union of cavum septi pellucidi and the cavum Vergae. (Diagram after Dandy,[22] page 49.)

C, position of noncommunicating cyst of the cavum septi pellucidi in relation to the ventricular system. (Diagram after Dandy,[22] page 48.)

of the cavum septi pellucidi and cavum Vergae which produced no symptoms, the larger cysts are invariably associated with neurologic signs or symptoms. This

is an important and logical point in differential diagnosis, inasmuch as the cyst should exert no pressure if it is in free communication with the ventricular system.

The following pneumoencephalographic features in the differential diagnosis of cyst of the cavum septi pellucidi and agenesis of the corpus callosum are taken largely from the thesis of Kunicki and Chorobski,[31] with additions by us.

A. Noncommunicating, fluid-filled cyst of the cavum septi pellucidi.

1. The anterior horn and the body of the lateral ventricles may or may not be separated. Their mesial walls may be merely invaginated, without separation.

2. There is no central shadow of air between the lateral ventricles (fig. 3 *A*).

3. The third ventricle cannot rise to the height present in cases of agenesis of the corpus callosum because the cyst of the cavum septi pellucidi prevents its ascent.

4. In an encephalographic examination, pressure of the cyst of the cavum septi pellucidi on the foramen of Monro might prevent drainage of the lateral ventricles, which therefore would not be visualized (fig. 4 *C*).

B. Communicating cyst of the cavum septi pellucidi.

1. The lateral ventricles are not separated and do not have a filling defect in their mesial walls.

2. No enlargement of the cyst or the ventricles is present, unless as a part of general hydrocephalus.

C. Cyst of the cavum septi pellucidi communicating with one lateral ventricle.

The shadows of air in the lateral ventricles will approach each other in the midline, the separating, unperforated wall of the cavum either being vertical or deviating from the ventricle containing air under a higher pressure toward the ventricle in which the pressure of air is lower.

REPORT OF CASE

History.—A single white man aged 39, the youngest of 7 children, was born after a normal uneventful labor, without recourse to instruments. There was no history of a resuscitation problem following birth or a feeding problem in the first five months of life. No abnormalities of physical or mental development were observed in early infancy. After a siege of severe diarrhea his first convulsion occurred at 5 months of age, coincident with sudden weaning at the time of his mother's death. The seizures, of a minute's duration, occurred once a month, were always nocturnal and were characterized by a generalized tonic and clonic convulsion and unconsciousness, without loss of sphincter or bladder control.

After the age of 20 years his seizures became generalized and tonic but invariably occurred in the daytime. The attacks were preceded by general irritability and an aura of nausea, right frontal headache and involuntary swallowing. If he was lying down before an attack he would rise to his feet, if he was standing he would kneel on his right knee. The seizures usually lasted about a minute. If not supported, he was apt to fall, and during one episode his clavicle was fractured. After an attack he frequently wandered about aimlessly in a disoriented manner, being able to open and close doors, and was silent and apparently oblivious to any one's addressing him. On his regaining insight and resuming his work, he suffered only a right frontal headache and recalled nothing of the spell except the aura.

Within two days of his vaccination for smallpox, at 6 years of age, he had about twenty generalized grand mal seizures, each of a minute's duration. In his opinion, periods of transient loss of memory followed this episode and have persisted up to the present. In school he had no particular difficulty in preparing or understanding his lessons. In the classroom, however, when he was called on to recite, he often forgot subject matter which he had memorized the night before. His humiliation was increased when after school the knowledge would return. Eventual retention of facts was normal. His grades were good in mathematics and grammar,

31. Kunicki, A., and Chorobski, J.: Ventriculographic Diagnosis of Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. **43**:139 (Jan.) 1940.

but he failed in history and geography. He stopped school after the seventh grade. He had been employed by a city illuminating company for twenty-three years. The company, fearing that he might be injured during a spell, transferred him from his former position as an expert linesman to that of a ground worker. Transient loss of memory had disturbed him. On many occasions he had forgotten orders and even had to return to his foreman to inquire about the nature of a task assigned to him. He stated that he sometimes staggered and seemed to be in a fog, when he could not recall instructions. He had been able to conceal the fact of his memory difficulty from his family up to the time of admission.

His sister related that she met him one evening at a railroad station and noted that he maintained a strange, blank facial expression while she drove him home. During this time he answered questions but offered no leading conversation. On their arriving home he could remember nothing of the journey with his sister.

The patient had a good disposition, was well liked by his friends, was intelligent and had a remarkably good insight into his own problem. He was, however, given to moods of depression concerning the futility of his life. He was hospitalized on Oct. 12, 1942 because of the increasing intensity of frontal headaches and convulsions during the preceding month.

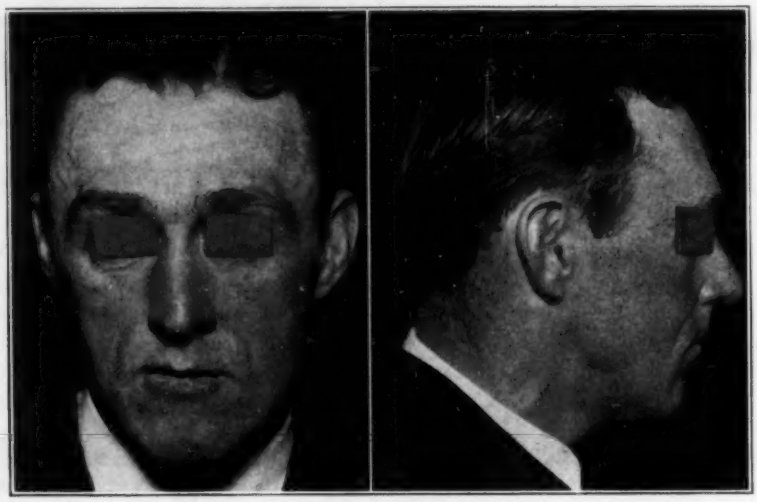

Fig. 5.—Front and side views of C. H. (present case).

Medical History.—He had attacks of measles, mumps and chickenpox during childhood. A tonsillectomy was performed in 1930. The results of studies of the spinal fluid made at another institution in 1930 were reported to be normal.

Family History.—An older sister died at the age of 3 years, of "brain fever." She was well until two days before her death, when she had a convulsion, followed by prolonged coma.

General Examination.—The patient presented an average, normal appearance and seemed well nourished and well developed (fig. 5). Aside from poor teeth, no abnormalities were seen. Neurologic examination gave entirely negative results except for a suggestion of adiadokokinesis in the left hand. Examination of the visual fields revealed concentric contraction to form and color in both eyes, most marked in the left eye. Early edema of the optic disk of the right eye and definite edema of the disk of the left eye were present and were thought to be due to low grade or long-standing increased intracranial pressure.

Encephalographic Study.—An encephalographic test was made on Oct. 21, 1942. The initial pressure was 515 mm. of water, with the vertex level at 770 mm. The pressure rose to 595 mm. of water after the injection of 10 cc. of air; 192 cc. of spinal fluid was then removed, and 197 cc. of air was injected into the subarachnoid space. The report on the spinal fluid was as follows: The fluid was clear and contained no cells and no globulin; the total protein content measured 30 mg. per hundred cubic centimeters; the Wassermann and Kahn reactions were negative and the colloidal gold curve was normal.

The encephalogram (fig. 6) revealed no abnormalities of the skull. In the anteroposterior view the lateral ventricles were considerably dilated and widely separated and had a bat wing

appearance. In the lateral view the lateral ventricles were dilated, particularly in their posterior horns. In the anteroposterior view the third ventricle was dilated, measuring 2 by 3 cm. on the roentgenogram. Its location was higher than normal, and its dome rose well above the foramens of Monro. The characteristic appearance of the third ventricle, which has been referred to as that of a "cocked hat," was seen in the lateral exposure. The interventricular foramens were elongated and widely dilated. A definite, sharply demarcated area of diminished density was seen above the third ventricle and between the lateral ventricles in the posteroanterior view and was clearly localized in the frontal area in the lateral view. This area measured 3 by 4 cm. on the encephalogram and may have been a porencephalic cyst. Extending in tentacle-like fashion was a narrow, air-containing channel appearing as a bridge between the cyst and the third ventricle. Close stereoscopic examination, however, revealed that it was most probably a distorted mesial cerebral sulcus (indicated by *A*, fig. 6*C*).

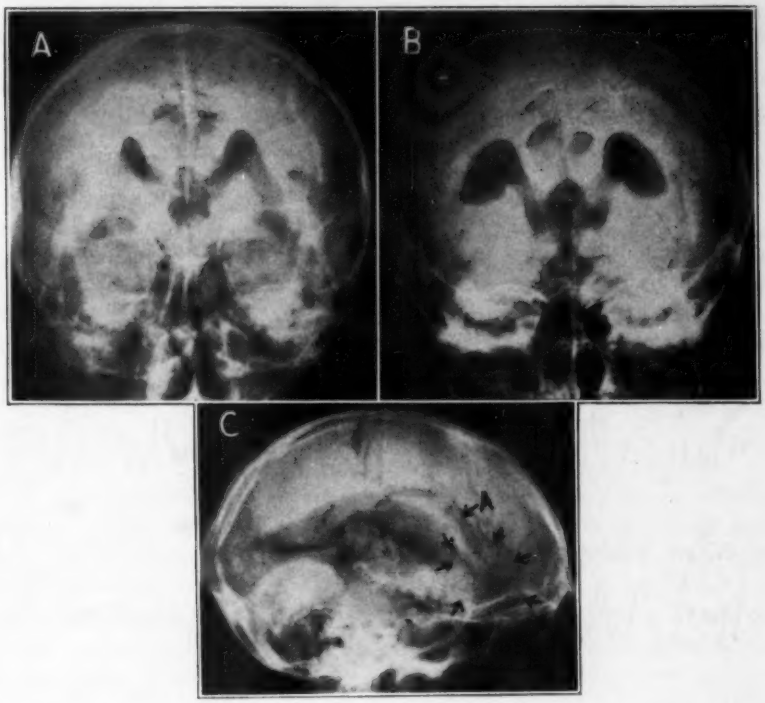

Fig. 6.—Encephalograms in present case. *A*, posteroanterior and, *B*, anteroposterior view. *C*, lateral view. Arrows denote periphery of a possible porencephalic cyst.

After the encephalographic examination the patient experienced severe headache, out of proportion to that usually following the procedure. Within five days this had subsided, and during the next month he was almost asymptomatic and had no convulsions. Within two months his seizures recurred and required sedation. After nine months the headaches were mild and infrequent. The convulsions, however, were similar to those before the examination but responded well to sedation therapy. An understanding of the clinical course is important in a differentiation of the lesion in this case from a noncommunicating cyst of the cavum septi pellucidi. Inasmuch as symptoms continued after encephalographic examination, it seems probable that this case was not one of noncommunicating cyst of the cavum septi pellucidi which ruptured spontaneously during the encephalographic procedure. Had this occurred the patient should have been relieved of his symptoms.

Electroencephalographic Study.—Bipolar recording was performed on Jan. 22, 1943; the monopolar method was used on March 18 by Dr. E. M. Zucker, of Cleveland City Hospital, who also interpreted the tracings (fig. 7). With the bipolar method leads were taken from the frontal, precentral, postcentral and occipital regions, high and low along each side. Channel 1

was between the frontal and the precentral region; channel 2, between the precentral and the postcentral region, and channel 3, between the postcentral and the occipital region.

Low along the right side there was little alpha rhythm except in channel 3, where there were fairly constant 9 to 11 per second waves with an amplitude of about 20 microvolts. There was a rapid, low voltage (28 to 30 per second) rhythm in all leads. Several random slow waves of about 20 to 30 microvolts appeared in channel 1. High along the right side were numerous 3 to 4 second waves. In channel 3 there was fairly regular alpha rhythm.

High along the left side slow waves were frequently encountered in channel 1. In channel 2 little alpha activity was present, there being low voltage, fast waves not unlike beta activity. Again, channel 3 showed a dominant alpha rhythm. The activity in the three channels low along the left side was much the same as that high along the same side.

The transfrontal channels showed constant fast waves of low amplitude and irregular slow waves, especially from the channel across the midline and on the left side. The transprecentral channel was similar to the transfrontal channels, with beta waves and random slow waves predominant from the left side and across the midline. The transpostcentral channel showed some 9 to 11 per second waves, with superimposed beta activity. The transoccipital leads

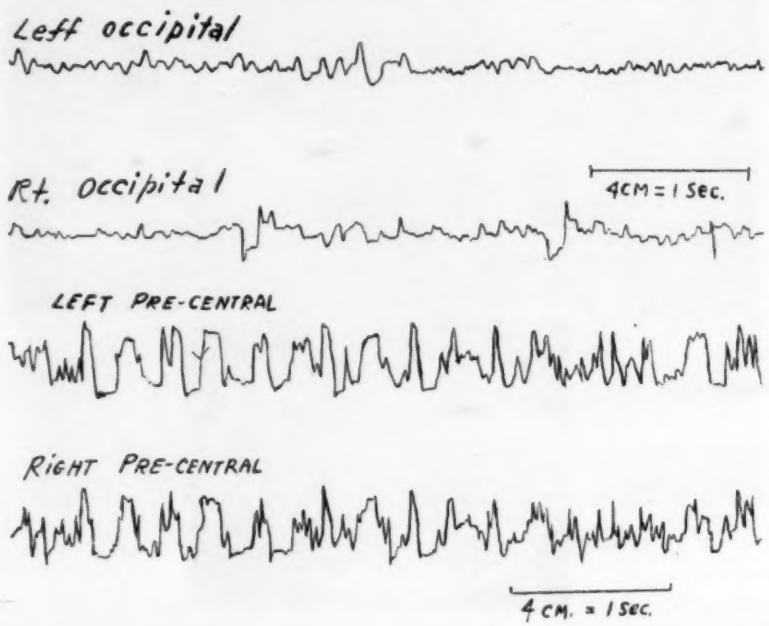

Fig. 7.—Monopolar method of recording brain waves by electroencephalography. Above: asynchronization of waves between the left and the right occipital lobe with the patient's eyes open. Note absence of normal alpha rhythm. Below: Fairly good synchronization between the left and the right precentral area.

showed fairly normal alpha waves from the right side and across the midline. The channel between the two occipital electrodes on the left side showed less alpha rhythm.

Monopolar recordings were made from the occipital, the postcentral, the precentral and the frontal region. Simultaneous records were taken from corresponding areas of the two sides. In records taken from the same side there was little difference between the frontal, the precentral, the postcentral and the occipital lead. There was definite dysrhythmia in all leads on both sides, more severe on the left. In a comparison of activities from the two sides in corresponding regions taken simultaneously, there appeared to be synchronization except in the record taken from the two occipital regions with the patient's eyes open.

Conclusion.—These electroencephalograms were definitely abnormal. They were characterized chiefly by irregular slow waves and absence of normal alpha activity. There was a continuous diffuse dysrhythmia, somewhat more severe on

the left. No phase reversal was observed in the bipolar method which could be used to localize definitely a cortical defect. With the monopolar recording there appeared to be good synchronization between the two sides except between the two occipital regions when the eyes were open.

This is the third case of agenesis of the corpus callosum on record in which electroencephalographic tracings have been made. Discussions of the electroencephalographic pattern in cases of agenesis of the corpus callosum reported independently in 1941 by Derbyshire and Evans [32] and by Goldensohn and associates [33] offer a few points for comparison with the tracings in this case. Derbyshire and Evans found instability of alpha rhythm similar to that in the tracing here reported. They also observed another point of similarity in that synchronization between the hemispheres was fairly good except between the occipital lobes. These authors made the assumption that during repose much of the linkage between the hemispheres could be effected by way of the interthalamic connections, the presence of a corpus callosum for synchronization of electroencephalographic patterns between the hemispheres thereby being made unnecessary. Opposed to this evidence is the report of Goldensohn and associates,[33] in whose case a striking absence of synchronism in electrical activity between the left and the right hemisphere, particularly in the occipital region, was observed. In all 3 cases the greatest dysrhythmia was observed between the occipital lobes. In 2 of these cases this occurred with the patient's eyes open. The obvious conclusion from the evidence so far submitted is that there is no characteristic electroencephalographic pattern by which a diagnosis of agenesis of the corpus callosum can be made. When the evidence from such tracings in many other cases has been summarized, further interesting knowledge concerning the function of the corpus callosum should be available.

SUMMARY

1. A case of agenesis of the corpus callosum diagnosed by encephalographic means during the life of a patient is reported. It is the fifteenth such case to be reported in the English literature. The presence of associated porencephaly is suggested in this case.

2. The pneumoencephalograms show dilated lateral and third ventricles, with a "bat wing" appearance in the posteroanterior view. The location of the third ventricle was higher than normal, and the foramens of Monro were widely dilated and elongated.

3. The electroencephalographic pattern in this case is definitely abnormal but cannot be considered as diagnostic of agenesis of the corpus callosum. It is characterized by irregular slow waves, absence of normal alpha activity and continuous diffuse dysrhythmia.

32. Derbyshire, A. J., and Evans, W.: A Case of Agenesis of the Corpus Callosum: Encephalographic Studies, Harper Hosp. Bull. **1**:17, 1941.

33. Goldensohn, L. N.; Clardy, E. R., and Levine, K.: Agenesis of the Corpus Callosum: Report of a Case with Neuropsychiatric, Psychologic, Electroencephalographic and Pneumoencephalographic Studies, J. Nerv. & Ment. Dis. **93**:567, 1941.

PROTECTIVE BARRIERS OF THE CENTRAL NERVOUS SYSTEM

AN EXPERIMENTAL STUDY WITH TRYPAN RED

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AND
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Knowledge of the normal physiology of the blood-brain barrier and of its alteration in diseases of the central nervous system constitutes one of the interesting advances in the field of neurology in recent years. Numerous studies on infectious, toxic, degenerative and post-traumatic diseases of the central nervous system indicate that the permeability of the blood-brain and the blood–cerebrospinal fluid barrier is more or less uniformly increased in these conditions.[1] The blood–cerebrospinal fluid barrier has been shown to be impaired after such procedures as the pneumoencephalographic test, lumbar puncture, induction of spinal anesthesia, intrathecal therapeutic injection and ventriculographic examination.[1] Technics involving such procedures have even been advocated to increase the efficacy

This study was made possible by a grant from the Christine Breon Fund.

From the Department of Surgery and the Spectrographic Laboratory of the University of California Medical School.

1. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood: A Physiological and Clinical Study, Baltimore, Johns Hopkins Press, 1935.

This review by Katzenelbogen is good, but by no means complete. Additional references of value with respect to the alteration of the permeability of the blood-brain barrier as a result of infectious processes are: MacCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. **49**:1695, 1912. McClellan, R. H., and Goodpasture, E. W.: A Method of Demonstrating Experimental Gross Lesions of Central Nervous System, J. M. Research **44**:201-206, 1923. Faber, H. K.: Visualization of Preparalytic Lesions of Poliomyelitis by Intravital Staining, Proc. Soc. Exper. Biol. & Med. **35**:10-12, 1936; The Early Lesions of Poliomyelitis After Intranasal Inoculation with Comments on Their Relationship to the Early Clinical Manifestations and to the Nonparalytic Cases, J. Pediat. **13**:10-37, 1938.

With respect to similar changes associated with post-traumatic conditions, the following references should be included: Barbour, H. G., and Abel, J. J.: Tetanic Convulsions in Frogs Produced by Acid Fuchsin and Their Relation to the Problem of Inhibition in the Central Nervous System, J. Pharmacol. & Exper. Therap. **2**:167-199, 1910. Abel, J. J.: On the Action of Drugs and the Function of the Anterior Lymph Hearts in Cardiectomized Frogs, ibid. **3**:581-608, 1912. McCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. **49**:1695, 1912. Sauerbruch, F.: Experimentelle Studien über die Entstehung der Epilepsie, Verhandl. d. deutsch. Gesellsch. f. Chir. **42**:144-149, 1913. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353-394 (April) 1920. Dandy, W. E., and Elman, R.: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. **36**: 40-49, 1925. Morgenstern, S., and Birjukov, M.: Weitere experimentelle Ergebnisse zur Frage der Permeabilität der Gehirncapillaren, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:640-650, 1928. Sawyer, W. A., and Lloyd, W.: The Use of Mice in Tests of Immunity Against Yellow Fever, J. Exper. Med. **54**:533-555, 1931. Lennette, E. H., and Hudson, N. P.: Blood-Central Nervous System Barrier in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **34**:470-472, 1936. Burnet, F. M., and Lush, D.: Infection of the Central Nervous System by Louping Ill Virus, Australian J. Exper. Biol. & M. Sc. **16**:233-240, 1938. Browman, T.: Ueber die Farbindikatormethode als tierexperimentelle Funktionsprobe des Bluthirnschrankensystems, Skandinav. Arch. f. Physiol. **80**:59-79, 1938.

of therapeutic agents which otherwise do not reach the central nervous system in effective concentrations.[1] For the most part, these studies have involved measurements of the permeability of the blood–cerebrospinal fluid barrier, and the question has been raised whether such determinations have any bearing on possible concomitant alterations in the permeability [2] of the blood-brain barrier. Since knowledge in this respect is inadequate and evidence [3] has been adduced which suggests that the blood–cerebrospinal fluid barrier and the blood-brain barrier are not comparable, but may be quite different in their permeability characteristics, the value of many of the older studies in this field has been questioned.

Although the importance of an impaired barrier in diseases of the central nervous system of toxic origin is unquestioned, the significance of similar changes occurring in infectious and post-traumatic conditions of the central nervous system remains unknown. Correspondingly, the possible therapeutic value of mechanisms which might maintain or lower the permeablity of the blood-brain barrier can only be conjectured. Such therapy for toxic conditions of the central nervous system would presumably be of major importance. For post-traumatic and infectious diseases of the central nervous system such therapy also might conceivably be of value. Knowledge of these therapeutic possibilities, however, is negligible. Aside from the possible effect of roentgen therapy [4] and the supravital dye brilliant vital red,[5] no method of lowering the permeability of the blood-brain barrier or of preventing its impairment in disease appears to be known.

The studies on brilliant vital red, carried out both on experimental animals and on patients in convulsive states, showed that the effect of the dye in lowering the permeability of the blood-brain barrier was associated with its protective action.[5] The evidence rested chiefly on the fact that in cases of experimental epilepsy brilliant vital red afforded protection against various epileptogenous agents and that direct spectrophotometric determinations showed that it lowered the permeability of the blood–cerebrospinal fluid barrier to cocaine hydrochloride. Since it was proved that the supravital dye had no central effect on the central nervous system and no peripheral effect in neutralizing or bonding with the convulsive agents, it was postulated that the action of the dye on the blood-brain barrier was similar to its measured effect on the blood–cerebrospinal fluid barrier. The fact that brilliant vital red is an acid dye and stains intensely the endothelium of both the blood–cerebrospinal fluid and the blood-brain barrier further contributed to this conclusion. Direct proof for this thesis, however, was lacking.

With these points in mind, the following studies were made in the hope of clarifying the relation between the blood–cerebrospinal fluid and the blood-brain barrier and of gaining further knowledge of the mechanisms of possible therapeutic value in lowering the permeability of these barriers.

PRELIMINARY STUDIES

In a trial of various representative supravital dyes, including brilliant vital red, congo red, trypan blue, methylene blue (methylthionine chloride) and eosin, brilliant vital red, and possibly congo red, were found to protect against the

2. Permeability is a much abused term. As used here in its broad sense, it refers to the selective transfer of metabolites in solution across a tissue membrane.

3. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125-145, 1942.

4. Spiegel, E. A., and Quastler, H.: Experimentelle und klinische Untersuchungen über dem Einfluss von Röntgenstrahlen und Diathermie auf die Durchlässigkeit der Blut- Liquor-Schranke, Wien. med. Wchnschr. **31**:1059-1061, 1931.

5. Aird, R. B.: Mode of Action of Brilliant Vital Red in Epilepsy, Arch. Neurol. & Psychiat. **42**:700-723 (Oct.) 1939.

convulsive effects of strychnine sulfate, picrotoxin and cocaine hydrochloride. In another study trypan red gave striking protection against the convulsive effects of cocaine hydrochloride. The susceptibility of white mice to convulsions induced by cocaine hydrochloride was determined on a statistical basis by methods similar to those used in previous studies.[6] The criteria of convulsive involvement were the same, and susceptibility was recorded as the most severe stage attained by each mouse within a period of observation of two hours. In a second series of

TABLE 1.—*Protective Effect of Trypan Red in Experimental Epilepsy Induced in White Mice* *

Number of Injections †	Number of Mice Tested	Convulsive Effects			Convulsions and Death	Convulsive Involvement, Percentage
		None	Petit Mal	Grand Mal		
0	233	67	46	58	62	71
1	32	17	5	9	1	47
2	31	21	5	3	2	32
3	29	24	1	4	0	17
4	82	72	6	3	1	12
5	40	34	4	2	0	15
3 or more	151	130	11	9	1	14

* Induced by injection of 96 mg. of cocaine hydrochloride per kilogram of body weight.
† Each injection consisted of 0.1 cc. of a 1 per cent solution of trypan red, given intraperitoneally on separate days. The cocaine test was performed the second day after the final injection of trypan red.

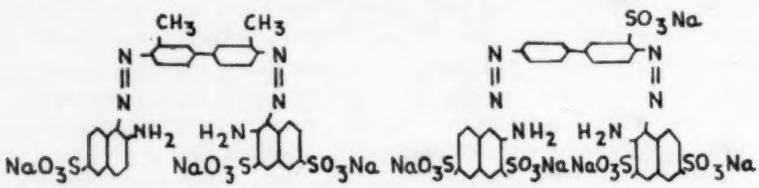

Fig. 1.—Structural formulas for brilliant vital red (C. I. no. 456), at left, and for trypan red (C. I. no. 438), at right.

experiments, white mice were given, on successive days, intraperitoneal injections of 0.1 cc. of a 1 per cent solution of trypan red (table 1), which resulted in various intensities of staining, as observed in the skin and scleras. These mice were tested with cocaine hydrochloride two days after the final injection of the dye, the dose of cocaine and conditions other than the staining being identical with those of the control group. Three or more injections of trypan red gave excellent protection over the two hour test period.

REVIEW OF LITERATURE AND HISTOLOGIC STUDIES ON TRYPAN RED

Trypan red, the pentasodium salt of o-benzidine monosulfonic acid bisazodi-2-napthylamine-3, 6-disulfonic acid, is an acid dye of the diazo series. Structurally and chemically it is closely related to brilliant vital red (fig. 1).

Trypan red has long been used as a supravital dye.[7] It is also of interest that Ehrlich and Shiga [8] introduced its use as a therapeutic agent for trypanosomiasis.

6. (*a*) Aird, R. B., and Gurchot, C.: Protective Effect of Cholesterol in Experimental Epilepsy, Arch. Neurol. & Psychiat. **42**:491-506 (Sept.) 1939. (*b*) Aird.[5]

7. Conn, H. J.: Biological Stains, Geneva, N. Y., Biotech Publications, 1940.

8. Ehrlich, P., and Shiga, K.: Farbentherapeutische Versuche bei Trypanosomenerkrankung, Berl. klin. Wchnschr. **41**:329-332 and 362-365, 1904.

Various toxicologic investigations have been carried out on trypan red. It has been shown that this dye acts on the hematopoietic activities of the reticuloendothelial system.[9] Repeated injections in white rats produced anemia, a percentile rise in the reticulocytes, marked neutrophilic leukocytosis, granuloblastic hyperplasia and the formation of macrophages in proportion to the destruction of erythrocytes in the spleen and bone marrow. Single intraperitoneal injections of 1 cc. of a 1 per cent solution, however, produced little or no change. The lethal dose by intravenous administration in dogs was shown by Risi [10] to be approximately 80 mg. per kilogram of body weight. Lewis [11] found that slow intravenous injection of 100 cc. of a 0.25 per cent solution of trypan red in rabbits gave no ill effects, either early or late. Intravenous injections of less than 25 mg. per kilogram of body weight appear to be well tolerated. Because of the slow elimination of the dye from the tissues, an intense stain is achieved with relatively few injections and may be maintained with one injection per month, or even fewer.

Histologic studies [12] indicated that dyes of the benzidine group stain deeply, and with a fairly high degree of selective specificity, certain cells of the body: the connective tissue clasmatocytes, the macrophages of serous cavities and the endothelial cells. That these cells react intensely to the dye was indicated by the storage in their cytoplasm of large and brilliant "dye granules." The blood cells, the epithelium, the central nervous system, except for the vascular elements (choroid plexus and intracerebral blood vessels), and the meninges, however, showed no evidence of the dye.

Gross and histologic studies on mice and cats stained with trypan red amply confirmed these observations. While typical intracellular deposits appeared in the endothelial cells of the choroid plexus and brain, the ependyma, the cerebrospinal fluid and the cortical tissues failed to show any trace of the dye. In general, the results closely paralleled those obtained by staining with [brilliant] vital red.[5]

SPECTROCHEMICAL STUDIES

A more accurate evaluation of the effect of trypan red on the permeability of the blood-brain and blood–cerebrospinal fluid barriers seemed desirable. This proved feasible with the use of a spectrochemical technic which my associates and I [13] recently devised for following the distribution of cocaine throughout the body.

METHODS

Cats were used as experimental animals, inasmuch as mammals fairly high in the phylogenetic series and of moderate size (from 2 to 4 Kg. in weight) are desirable for such a study. Cocaine hydrochloride was selected as the convulsive agent because of its effect on

9. Latta, J. S., and Moore, F. H.: The Interpretation of Changes Resulting in Anemia Induced by the Intravital Dye, Trypan Red: Experimental Evidence Supporting the Monophyletic Theory of Blood Cell Origin, Folia haemat. **48**:178-209, 1932.

10. Risi, A.: Sulla chemioterapia della sostanze coloranti: Ricerche tossicologiche sul trypanrot—trypanblau e wasserblau, Rassegna di terap. e pat. clin. **5**:491-546, 1933.

11. Lewis, P. A.: The Distribution of Trypan Red to the Tissues and Vessels of the Eye as Influenced by Congestion and Early Inflammation, J. Exper. Med. **23**:669-676, 1916.

12. Evans, H. M., and Schulemann, W.: The Action of Vital Stains Belonging to the Benzidine Group, Science **39**:443-454, 1914. Evans, H. M.: The Physiology of Endothelium, Anat. Rec. **8**:99-101, 1914.

13. Strait, L.; Aird, R. B., and Weiss, S.: A Method for the Rapid Isolation and Spectrographic Measurement of Cocaine from Brain Tissue, J. Pharmacol. & Exper. Therap. **73**:363-374, 1941.

the higher cortical centers[14] and its characteristic spectral absorption,[15] which permits the detection and measurement of minute amounts with accuracy.

Narcosis was essential, as the experiments required that somewhat complicated procedures be carried out accurately on a set time schedule. Five cats were anesthetized by the intraperitoneal injection of 20 mg. of chloralose (a compound of chloral hydrate and dextrose) per kilogram of body weight, followed after forty-five minutes by 0.2 cc. of paraldehyde per kilogram. The narcosis induced varied from light to moderately deep anesthesia, the average effect in the group being adequate but not deep. Chloralose and paraldehyde were used because of their antagonistic effects on the convulsive threshold, so that when administered in combination in the doses mentioned they produce little or no alteration of the convulsive threshold, as determined by electrical stimulation.

The experimental basis for this phase of the study was established by determination of the convulsive threshold of cats to electrical stimulation under various conditions, as shown in table 2. An alternating current of 60 cycles, controlled by rheostat and variac transformer, was used as the stimulus and was measured by a highly damped thermocouple milliammeter. The duration of stimulation was one second. Needle electrodes, placed with antiseptic technic, were used to avoid difficulties which might arise from great variations in cutaneous resistance. One needle was placed across the midline of the scalp over the region of the motor cortex, and the second, in the anterior portion of the neck.

TABLE 2.—*Convulsive Threshold to Electrical Stimulation of Cats Under the Influence of Various Anesthetics and Without Anesthesia*

Anesthetic	Dose per Kg.	Narcotic Effect	Number of Cats	Number of Tests	Range of Convulsive Thresholds, Ma.	Average Convulsive Threshold, Ma.
Ether	.....	Light	7	7	70-100	84
*Pentobarbital	26 mg.	Light	4	4	41- 64	52
*Paralydehyde	1 cc.	Moderate to deep	12	28	32-116	57
	0.2 cc.	Light	3	3	32- 49	41
*Chloralose	80 mg.	Deep	4	4	3- 37	14
	20 mg.	Light	3	3	13- 14	13
*Paraldehyde and Chloralose	0.2 cc. 20 mg.	Moderate	12	46	26- 77	40
No anesthetic	.....	.....	5	8	24- 66	40

* Injected intraperitoneally.

Additional studies were made to determine the effect on susceptibility to convulsions of the combined chloralose and paraldehyde anesthesia. Experimental epilepsy was induced in white mice by the use of cocaine hydrochloride under the same conditions as those observed in the previous studies of this type. One hour before injection of the cocaine hydrochloride, a test group of cats were given, by intraperitoneal injection, 20 mg. of chloralose per kilogram of weight; forty minutes later 0.2 cc. of paraldehyde was administered to the same animals by intraperitoneal injection. The results obtained in this group were then compared with those observed in previous control groups of animals to which no anesthetic had been given. The results, shown in table 3, indicated that in spite of a light anesthetic effect on the test group, there was no appreciable variation of the convulsive threshold in the two groups as determined by this technic. Since anesthesia as used in this study produced no significant alteration of the convulsive threshold either to electrical stimulation or to drugs and since all the experiments were done under identical conditions in this respect, it was assumed that the results obtained were not influenced by this phase of the procedure.

Twenty minutes after the injection of the paraldehyde, the administration of the epileptogenous agent was started. Twenty milligrams per kilogram of body weight of a 6 per cent solution of cocaine hydrochloride was injected continuously and evenly over a period of fifteen minutes by way of the left femoral vein. Although such a dose of cocaine hydro-

14. Feinberg, I.: Weitere Mittheilungen zur physiologischen Cocainwirkung, Berl. klin. Wchnschr. **24**:166-168, 1887. Morita, S.: Untersuchungen an grosshirnlosen Kaninchen: II. Die Wirkung verschiedener Krampfgifte, Arch. f. exper. Path u. Pharmakol. **78**:208-217, 1915.

15. Castille, A.: Ultra-Violet Absorption Spectra of the Alkaloids of the Tropeine Group, Bull. Acad. roy. de méd. de Belgique **5**:193-200, 1925.

chloride is well within the ordinary convulsive range of this drug, even mild convulsive effects were observed but rarely with the slow rate of injection used. The slow injection allowed time for the cocaine to become distributed throughout the body, with a minimal loss by way of the kidney. After completion of the injection of the convulsive agent, specimens of the cerebrospinal fluid, the motor cortex and the blood were obtained at intervals of five minutes.

From 2 to 3 cc. of cerebrospinal fluid was obtained from each cat by cisternal puncture, care being taken to avoid bloody taps or contamination of the specimen by blood. This fluid was collected in a large pyrex tube and immediately frozen by insertion of the tube into carbon dioxide snow.

TABLE 3.—*Susceptibility of White Mice to Convulsions Induced with Cocaine Hydrochloride* * Under Control and Anesthetic Conditions*

	Number of Mice	Effects				Convulsive Involvement, Percentage
		No Convulsions	Petit Mal	Grand Mal	Fits and Death	
Control group (no treatment)....	86	20	14	18	34	77
Group under anesthesia †.....	60	7	20	27	6	88

* 96 mg. per kilogram of body weight injected subcutaneously.
† Anesthesia induced by intraperitoneal injection of 20 mg. of chloralose (compound of chloral hydrate and dextrose) per kilogram of body weight (one hour before injection of cocaine) and 0.2 cc. of paraldehyde per kilogram (twenty minutes before injection of cocaine).

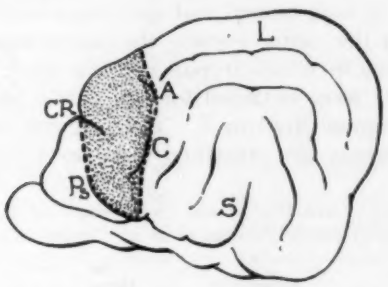

Fig. 2.—Left cerebral hemisphere of Felis domestica, showing the motor cortex and the suriace lines of excision.

CR indicates sulcus cruciatus; *A*, sulcus ansatus; *L*, lateral sulcus; *C*, sulcus coronalis; *Ps*, sulcus presylvius, and *S*, sulcus pseudosylvius.

Specimens of the motor cortex, weighing from 2 to 3 Gm., were obtained from the cerebral hemisphere of each cat. The portion of cerebral cortex obtained is shown in figure 2. This consisted of the gray matter of the lateral convexity of the cerebral cortex, bordering on the sulcus cruciatus and bounded posteriorly by the sulcus ansatus and sulcus coronalis and anteriorly and inferiorly by the sulcus presylvius.[16] The dissection was carried into the white matter but avoided inclusion of the caudate nucleus. The specimens were briefly washed with water and quickly dried on clean paper towels, care being taken to eliminate all blood on the surface. Immediately after being weighed, the specimens were immersed in liquid air.

Five cubic centimeters of blood was drawn by direct cardiac puncture, injected into a large pyrex tube and immediately frozen by insertoin of the tube into carbon dioxide snow.

Although artificial respiration was occasionally required toward the end of the period during which the specimens were obtained, all samples were taken while the heart was still active and the circulation adequate. The specimens from each of the 5 cats were mixed so that, finally, for each experiment they consisted of (1) from 10 to 15 Gm. of cerebrospinal fluid, (2) from 10 to 13 Gm. of motor cortex and (3) approximately 27 Gm. of blood.

16. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, Johann Ambrosius Barth, 1909. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

To determine the permeability of the blood-brain barrier to epileptogenous agents, such as cocaine, used experimentally, it became necessary to refine the technic of their extraction from the brain and to increase the accuracy of their measurement considerably beyond the point permitted by older methods. With spectrochemical methods a modified technic was developed which permitted the quantitative extraction and determination in vivo of as little as 0.1 mg. of cocaine from 12 Gm. of brain, with 95 per cent recovery and an estimated error of less than 10 per cent.[13] The spectrophotometric technic possesses the added advantage that spurious results may be ruled out, the cocaine being clearly distinguishable from undesirable contaminants which follow the process of extraction and which have limited the sensitivity and accuracy of other methods.

Determinations of the concentration of cocaine in the blood were obtained in order to rule out effects other than an alteration of permeability, such as hydrolysis of cocaine in the liver or alteration of permeability in other organs or tissues, with resulting loss of the cocaine, which conceivably might be regarded as an explanation of the results observed. On the assumption that cocaine is hydrolyzed in the central nervous system, one might explain the observed results in terms of an alteration in the rate of its hydrolysis. This would not appear to be a satisfactory explanation, however, in view of the relative stability of cocaine in the organism, the large alteration in the concentration of cocaine that was found (approximately one third of the total) and the brief period of experimentation in which such a change might have occurred. That such an agent as trypan red, which does not gain entrance to the central nervous system, could cause such an alteration in the hydrolysis of cocaine in the central nervous system appears further to render this explanation untenable.

RESULTS

From the standpoint of both animal and spectrochemical technics, satisfactory [17] results were obtained on the motor cortex, the cerebrospinal fluid and the blood in all 5 of the experiments in which trypan red was used. Of 12 control experiments, satisfactory results were obtained for the motor cortex in 9, for the blood in 5 and for the cerebrospinal fluid in 7. The original data obtained from these experiments and the summary are presented in tables 4 and 5.

TABLE 4.—*Spectrochemical Determination of the Distribution of Cocaine Hydrochloride With and Without Treatment With Trypan Red*

Treatment	Experiment No.	Motor Cortex *	Blood *	Cerebrospinal Fluid *
None	1	84.5	†	†
	2	†	†	6.25
	3	56.9	13.8	10.85
	4	73.8	20.4	8.55
	5	84.0	†	8.9
	6	62.5	16.7	8.55
	7	60.4	†	8.15
	8	66.1	†	†
	9	52.8	13.6	8.65
	10	53.7	20.6	†
Four intraperitoneal injections of 5 cc. of 1% trypan red	1	46.3	14.4	6.12
	2	31.4	10.9	4.45
	3	43.6	14.0	5.14
	4	33.6	13.7	4.72
	5	32.7	14.7	4.96

* Milligrams of cocaine hydrochloride per gram of tissue × 1,000.
† The majority of these samples either were lost in the process of extraction or were discarded before measurement because of unsatisfactory absorption spectrums.

The statistical mean concentration of cocaine in the motor cortex of the cats which were not treated with trypan red was 0.066 ± 0.003 mg. per gram. The concentration in the motor cortex of the treated animals was notably lower, 0.038 ± 0.002 mg. per gram. The odds are about 375,000,000 to 1 that this alteration in value may be due to chance. In contrast to concentrations in the brain, those in the blood for both treated and untreated animals differed but

17. "Satisfactory" refers merely to the samples which were not lost in the course of the extraction or which were not discarded before measurement because they did not satisfy objective criteria for photometric determination.

slightly. The mean concentrations in the blood for untreated and treated animals were respectively 0.017 ± 0.001 and 0.014 ± 0.0005 mg. per gram. The odds of 24 to 1 that this difference was due to chance may be dismissed by statistical criteria. It is conceivable, however, that this slight difference, although of no importance to the conclusions reached here, may be real and indicative of a slight increase in renal excretion, due to a toxicity for the kidneys of the trypan red in the concentrations used in these experiments. The concentrations in the cerebrospinal fluid for the treated and the untreated animals were lower than the concentrations in the blood and brain;[18] they were respectively 0.0086 ± 0.00008 and 0.0051 ± 0.0002 mg per gram. As in the case of the motor cortex, the difference in concentration between the treated and the untreated group is great, and the odds against a chance result, 10^{23} to 1, are impressive.

A schematic representation of the data showing the relative distribution of cocaine and the alterations in the mean concentrations of cocaine in these experiments is given in figure 3. That the concentrations in the various tissues of the same animals lie within sharply defined boundary lines attests to the reliability

TABLE 5.—*Summary of Results and Statistical Analysis of Alteration of Permeability of Blood-Brain and Blood–Cerebrospinal Fluid Barriers to Cocaine Hydrochloride* After Treatment with Trypan Red*

Specimen	Treatment	Number of Experiments	Total Number of Cats	Arithmetical Mean, M (Mg./Gm. × 1,000)	Standard Deviation, σ	Standard Deviation of Difference, D	Significance Test U's — t's D	Odds †
Motor cortex	Treated ‡.....	5	25	37.52 (M_t)	2.8	4.95	5.77	$3.75 - 10^8$
	Untreated (control)	9	45	66.1 (M_u)	4.08			
Blood	Treated ‡.....	5	25	13.54 (M_t)	0.682	1.67	2.08	24
	Untreated (control)	5	25	17.02 (M_u)	1.52			
Cerebrospinal fluid	Treated ‡.....	5	25	5.08 (M_t)	0.285	0.31	11.24	Approximately 1×10^{23}
	Untreated (control)	7	35	8.56 (M_u)	0.121			

* 20 mg. per kilogram of body weight injected intravenously.
† Odds against the results being due to chance.
‡ Four daily intraperitoneal injections of 5 cc. of a 1 per cent solution of trypan red.

of the experimental results. Diagrammatically, this area is the equivalent of a uniform coefficient of variation of the mean values of concentration for each tissue and indicates a high degree of internal consistency for the data.

These results clearly indicate that in the presence of concentrations of cocaine in the blood which were essentially the same in groups of cats given trypan red and those not given the dye, significant alterations in the passage of cocaine through the blood-brain and the blood–cerebrospinal fluid barrier occurred after supravital staining with trypan red. The amount of cocaine reaching the motor cortex was reduced by approximately 31 per cent and that reaching the cerebrospinal fluid by 40 per cent in the cats treated with the dye as compared with similar groups of animals not so treated.

COMMENT

The parallelism between the related supravital dyes trypan red and brilliant vital red appears to be close. Both dyes stain intensely the endothelial components

18. The distribution of cocaine in the tissues and the possible significance of such data with respect to the pharmacodynamic action of cocaine will be given elsewhere.

of the blood-brain and the blood–cerebrospinal fluid barrier but do not stain the ependyma, the nerve tissue proper or the cerebrospinal fluid. Like brilliant vital red, trypan red protects in experimental convulsive states. In dogs the passage of cocaine across the blood–cerebrospinal fluid barrier was reduced approximately 40 per cent after they were stained with brilliant vital red.[5] Correspondingly, after cats were stained with trypan red, the amounts of cocaine which passed the blood-brain and the blood–cerebrospinal fluid barrier were lowered 31 and 40 per cent respectively. By analogy, then, the present results appear further to corroborate the conclusion reached in the study of brilliant vital red,[5] namely, that the dye significantly altered (lowered) the permeability of the blood-brain barrier.

Considerable evidence has been adduced with respect to the permeabilities of the blood-brain and the blood–cerebrospinal fluid barrier for dyes, drugs, toxins,

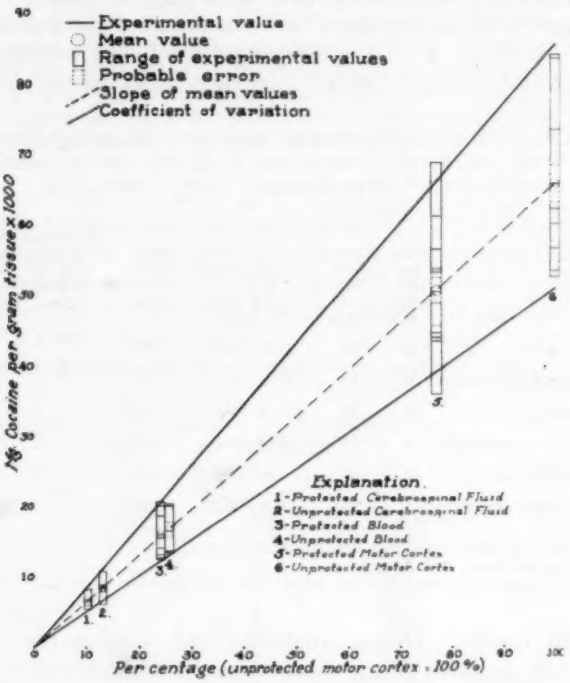

Fig. 3.—Spot graph of spectrophotometric determinations on groups of cats, treated with trypan red and without such treatment, showing the relative distribution of cocaine in the motor cortex and the cerebrospinal fluid, the range of variations in the determinations, the arithmetical means and probable errors of the determinations and the percentage of difference between the average amount of cocaine found in the tissues of animals treated with trypan red and the average amount in tissues of the animals which were not treated.

antibodies and viruses.[8] These studies have been interpreted as showing that these two barriers differ widely in their permeabilities, depending on the electrical charge of the permeating substance. Certain unexplained exceptions, however, have been noted. In this connection, it is of interest that in the present experiments the alkaloid cocaine, which presumably possesses the same electrical charge (probably positively charged in the basic blood stream) for both barriers, was found to pass both barriers. Furthermore, both barriers were modified in these experiments in the same direction, and roughly to the same degree, by the action of trypan red.

The fact that more cocaine was found in the brain than in the cerebrospinal fluid might be interpreted as indicating a difference in the permeability of the two barriers. The higher concentration of cocaine in the brain, however, may merely reflect the greater relative solubility of cocaine in the lipids of the brain than in the aqueously constituted cerebrospinal fluid or the blood, with its colloidal character.

The alterations in permeability of the blood-brain and the blood–cerebrospinal fluid barrier observed in this study, therefore, verify the hypothesis of Spatz [19] that the endothelium is the locus of the barrier between the blood and the central nervous system. Although these results contradict the beliefs expressed by Krogh [20] and Ehrlich,[21] who denied the existence of any selective capillary permeability, they are entirely in accordance with the position held by King.[22] King expressed the opinion that the permeabilities of the blood-brain and the blood–cerebrospinal fluid barrier are not necessarily different and explained the apparent difference in terms of the "affinity" of the brain in the case of the blood-brain barrier and its corresponding absence in the case of the blood–cerebrospinal fluid barrier.

Used in a broad sense, permeability refers to the selective transfer of metabolites in solution from the medium on one side of a tissue membrane to the medium on the other side. As indicated by the laws governing the Donnan equilibrium, and as recently shown by the interesting studies of Younge and Hurst,[23] the constitution of the mediums is an important factor and cannot be dissociated from the over-all consideration of the permeability of the membrane in its natural environment. For these reasons, even though the endothelial components of the blood-brain and the blood–cerebrospinal fluid barrier might be essentially identical, the permeabilities of these barriers are probably somewhat different. Owing to the presence of the brain and its attendant metabolic activity, the extracellular fluid of the brain is presumably considerably different from the cerebrospinal fluid, at least from the cerebrospinal fluid originating in the choroid plexus. The presence of the brain, then, might conceivably alter, indirectly but appreciably, the permeability of the blood-brain barrier from that obtaining in the blood–cerebrospinal fluid barrier. This alteration was inferred by King.[22]

It is important in this connection to define the term "blood-brain barrier." Although this term implies a single barrier between the blood and the brain, it is clear, as already indicated, that this appellation should be restricted to designate those structures which separate the blood from the extracellular fluid of the brain, namely, the endothelium of the capillaries supplying the brain together with their investing sheaths. The endothelium appears to be the important component of this barrier, inasmuch as the supravital dyes, brilliant vital red and trypan red, although modifying its permeability, do not gain entrance to the central nervous system in significant amounts and stain only the endothelium.

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19. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. f. Psychiat. **101**:267-358 1934.

20. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922, pp. 204-205.

21. Ehrlich, P.: Ueber die Berziehungen von chemischer Constitution, Vertheilung und pharmakologischer Wirkung, in Gesammelte Arbeiten zur Immunitätsforschung, Berlin, A. Hirschwald, 1904, p. 573.

22. King, L. S.: The Hematoencephalic Barrier, Arch. Neurol. & Psychiat. **41**:51-72 (Jan.) 1939.

23. Younge, C. M.: On the Nature and Permeability of Chitin: II. The Permeability of the Uncalcified Chitin Lining; The Foregut of Homarus, Proc. Roy. Soc., London s.B. **120**:15-41, 1936. Hurst, H.: Permeability of Insect Cuticle, Nature, London **145**:462-463, 1940; Insect Cuticle as an Asymmetrical Membrane, ibid. **147**:388-389, 1941.

It is suggested by these studies, as well as by anatomic and physiologic considerations, that the cell membranes of the cortical tissue form a second, and even more important, barrier, which may be termed the "cortical barrier." The interface between the lipoidal nerve tissue and the aqueous extracellular fluid undoubtedly possesses complex surface properties and semipermeable characteristics capable of the selective activity essential for function as a barrier. Since this barrier controls the transfer of metabolites concerned with the oxygenation and nutrition of the cells as well as the elimination of the waste products of cellular metabolism, it presumably plays a vital role in the physiology of the brain. A schematic representation of these barriers is shown in figure 4.

A considerable amount of the conflicting evidence adduced in the numerous studies which have been made on the blood-brain and the blood–cerebrospinal fluid barrier may be explained, in part at least, by the failure to consider this second, more central, barrier formed by the cell membranes of the cortical tissue. This is particularly true of those studies in which the interpretation of results depended on the effects of drugs on the cortex and which, therefore, directly

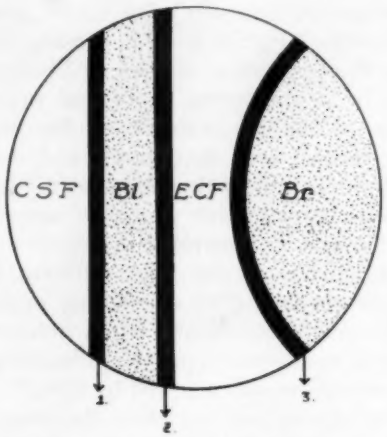

Fig. 4.—Schematic diagram of the blood-cerebrospinal fluid barrier (*1*), the blood-brain barrier (*2*) and the cortical barrier (*3*).

CSF indicates cerebrospinal fluid; *Bl*, blood; *ECF*, extracellular fluid of the brain, and *Br*, cellular constituents of the brain.

involved this cortical barrier. Much that King [22] would account for in terms of the "affinity of the nervous tissue" might be thus explained. It is not necessary to think of the cortical barrier alone as modifying the passage of drugs or of metabolites from the extracellular to the intracellular spaces. Equally important is any modification of surface properties, with a direct effect on cellular reactivity or secondary effects arising from the ability of centrally acting drugs to attach themselves to the cells. It is conceivable that the blood-brain barrier may be comparable to the blood–cerebrospinal fluid barrier but that, because of the secondary effects of the cortical barrier, experimental results on the two may appear to be very different. Such possibilities have not been properly emphasized in even the most recent review of literature concerned with the blood-brain barrier.[3]

The implications of the results of this study with respect to susceptibility to convulsions are the same as those discussed in the previous study on brilliant vital red.[5] It should be stressed, however, that, although the experimental approach used in this study depends on direct measurements of permeability and the posi-

tive results obtained may be interpreted as favoring a toxic factor in epilepsy, it should not be assumed that all forms of epilepsy are necessarily of this type. Knowledge of the various forms of the convulsive state suggests that this condition cannot be explained so simply.

The arguments in favor of a toxic form of epilepsy and the limitations of this concept need not be repeated. It is emphasized that numerous complex physiologic and biochemical changes are associated with an alteration of the semipermeable characteristics of the tissue membranes, and since these changes occur together, it is not possible to say that any single factor or combination of factors is responsible for any resulting physiologic effect. Water balance, shifts of acid-base balance and other factors affect the permeability of the tissue, and in turn are affected by such changes. Although the alteration of permeability in itself is presumably of the greatest importance in this study of epileptic convulsions induced by drugs, it is conceivable that one of the changes associated with this alteration may be the precipitating factor in human epilepsy. More likely still is the possibility that the convulsive state is a result of the whole complex of changes, that is, that the changes associated with increased permeability in cortical tissue cause a more unstable and irritable state, which, in turn, is characterized by an increased susceptibility to convulsions. As has been pointed out in previous articles,[6] those mechanisms which are known to increase the permeability of tissue, such as alkalosis, hydration, anoxemia and inflammatory changes, are also known to lower the convulsive threshold. As a single mechanism of fundamental neurophysiologic importance in determining cellular nutrition and reactivity, premeability, or rather the complex of changes associated with alterations of permeability, offers an attractive hypothesis for the numerous, and otherwise unrelated, factors known to be of importance in modifying convulsive reactivity.[6b]

A more obvious, and possibly more important, implication of this study lies in its possible therapeutic application to toxic and degenerative diseases of the central nervous system. It is conceivable that the vital dye might protect against other toxic disease of the central nervous system (retrobulbar neuritis; eclampsia; lead encephalopathy; arsenic poisoning), as well as against toxic convulsive states. In addition, various degenerative diseases of the central nervous system, which are known or assumed to have a toxic origin, such as amyotrophic lateral sclerosis, Landry's paralysis, progressive muscular atrophy and multiple sclerosis, might be benefited by such therapy. Cobb and associates [24] found that brilliant vital red protects against triphenylphosphite used as a convulsive agent. Studies by one of us (R. A.) and associates [25] indicated that triphenylphosphite is quickly hydrolyzed after its injection and that two distinct effects may be ascribed to its breakdown products. The phenol fraction produces early convulsive effects at the level of the cord, while the phosphorous acid fraction causes delayed degenerative effects in the cord and brain stem.[26] Regardless of these mechanisms of action, the fact remains that the supravital dye afforded protection against such toxic effects, both the early convulsive and the late degenerative complications. The therapeutic possibilities and importance of this discovery, therefore, appear to

24. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, J. Nerv. & Ment. Dis. **85**:438-441, 1937; Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156-1177 (Dec.) 1938.

25. Aird, R. B.; Cohen, W. E., and Weiss, S.: Convulsive Action of Triphenyl Phosphite, Proc. Soc. Exper. Biol. & Med. **45**:306-309, 1940.

26. Smith, M. I.; Lillie, R. D.; Elvove, E., and Stohlman, E. F.: The Pharmacological Action of the Phosphorus Acid Esters of the Phenols, J. Pharmacol. & Exper. Therap. **49**:79-99, 1933.

be considerable. The systematic clinical trial of these agents, or similar substances which may be discovered, seems to be justified. Such studies are now in progress. It is hoped that the present encouraging results will warrant a fuller and more comprehensive clinical report later.

SUMMARY AND CONCLUSIONS

Trypan red, a supravital diazo dye closely related to brilliant vital red, was found to parallel the latter in its staining properties and its physiologic effect in lowering the permeability of the blood-brain and the blood–cerebrospinal fluid barrier. The distribution of cocaine in the motor cortex, the cerebrospinal fluid and the blood of cats was accurately determined by spectrochemical methods under standard conditions. When similar groups of cats were stained with trypan red, the amount of cocaine entering the cortex was lowered by 31 per cent and that entering the cerebrospinal fluid was decreased by 40 per cent, while the concentration in the blood remained essentially the same.

The alteration in permeability of the blood-brain barrier associated with the selective staining of the endothelial elements of this barrier verifies the hypothesis of Spatz that the locus of the barrier between the blood and the extracellular fluid of the brain lies in the endothelium of the intracerebral vessels. The similar alteration in the permeability of the blood–cerebrospinal fluid barrier constitutes strong evidence in favor of the cogent arguments of King that the permeability of the endothelium of the blood–cerebrospinal fluid barrier is not necessarily different from that of the endothelium of the blood-brain barrier and emphasizes the importance of the brain in explaining apparent differences in the permeability of these two barriers. It is pointed out that the term "blood-brain barrier" is confusing and that, if the name is to be retained, it should be restricted to the barrier between the blood and the extracellular fluid of the brain. The presence of a third barrier, located in the cell membranes of the cortical tissue, is stressed.

The results obtained in this study suggest that changes in the permeabliity of the blood-brain and the cortical barrier, or factors associated with such changes, are of fundamental neurophysiologic importance in determining susceptibility to convulsions. Although these results, which depend on the induction of experimental epilepsy by convulsive drugs, might be interpreted as favoring the theory of a toxic origin of the convulsive state, it is suggested that any biochemical, neurophysiologic or neuropathologic change which modifies, either directly or indirectly, the permeability of the blood-brain barrier or the cortical tissue will have a corresponding effect on the susceptibility to convulsions.

In view of the fact that the permeability of the blood-brain barrier is increased in various diseases affecting the central nervous system, knowledge as to mechanisms which lower the permeability of this barrier may well prove to be of clinical importance. The therapeutic possibilities of such mechanisms are considerable, and their trial in treatment of toxic and degenerative conditions of the central nervous system appears to be justified.

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CEREBELLAR SYNDROME FOLLOWING HEAT STROKE

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The lethal effects of high body temperatures are well known; nevertheless, over brief periods the temperature may rise as high as 111 F., or even higher, with rapid and complete recovery. The period must be brief because at such high temperatures the pathologic alterations in the body cells rapidly become irreversible. The cells of the central nervous system are particularly susceptible to any prolonged nocive influence, such as anoxia, trauma, alcohol and bromide intoxication; hence it is not surprising to find that fever itself induces rapid and severe alterations. In this paper we shall point out that certain cells in the central nervous system are more liable to specific pathologic changes in that borderland of heat stroke between total death and total recovery. Numerous cases of so-called neurotic sequels to heat stroke have been reported, but few in which the pathologic process was so strikingly indicated by clinical symptoms pointing to cerebellar dysfunction as in the one (case 2) to be reported.

We have had the opportunity to survey the material in the Army Medical Museum, by permission of its curator, Colonel J. E. Ash, and have selected a case (Acc. 69622) of heat stroke in which the patient survived long enough to show beginning pathologic changes in the cerebellar ganglion cells (case 1).

REPORT OF CASES

CASE 1.—A 60 year old inmate of the Soldier's Home was admitted to the hospital on July 27, 1940, during a prolonged spell of very hot weather, because of sudden unconsciousness. His axillary temperature was 109 F. Physical examination revealed pinpoint pupils, hot and dry skin and absence of deep reflexes. In spite of intensive antipyretic measures, at the end of two hours his temperature was 106 F. He remained comatose. The following morning his temperature was 102 F. He died approximately twenty hours after admission.

Necropsy.—There were edema and congestion of the lungs, hypertrophy of the heart, chronic passive congestion of the liver, fibrosis of the spleen and cholelithiasis. The brain was swollen, and the cerebrospinal fluid was decreased. The vessels of the meninges, as well as those of the cortex and the basal nuclei, were congested. Section of the brain showed several small areas of old softening. Microscopic examination revealed generalized congestion and edema. The ganglion cells of the cerebral cortex were pale and swollen, with enlarged pericellular spaces, although their nuclei were usually still visible. The presence of some old arteriosclerotic lesions was verified. The arteries of the basal ganglia showed conspicuous infiltration of their walls with iron. Several small arteries in the vicinity of the third ventricle presented fresh ring hemorrhages. Sections of the cerebellum showed congestion with marked edema, especially of the molecular layer. The Purkinje cells were severely affected, many being absent and the rest in a state of coagulation necrosis, with loss of Nissl bodies and small opaque nuclei (fig. 1). The processes could be followed only a short distance. There was no cellular infiltration or glial reaction. The cells of the dentate nucleus were much less seriously affected, and those of the granule layer seemed only moderately damaged.

Brouwer,[1] in 1913, reported a case of a man aged 30, with no previous symptoms, who died while working in an overheated bakery. There was no record of this

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1. Brouwer, B.: Ueber Hemiatrophia neocerebellaris, Arch. f. Psychiat. **51**:539, 1913.

patient's temperature. Noteworthy postmortem observations were atrophy of the left cerebellar hemisphere to one-third the normal size and atrophy of the corpus dentatum, the cerebellar cortex and the pons on the opposite side. The actual lesion was confined to the cerebellar cortex, which showed pronounced atrophy to the molecular zone, the Purkinje cells being almost entirely absent and the granular layer reduced to a thin layer of rather large cells. In view of the unilateral changes, we believe this case may have been one of silent cerebellar hemiatrophy.

Schwab,[2] in 1925, reported autopsy observations on animals which had been exposed to radiating heat from the sun. There was generalized venous hyperemia,

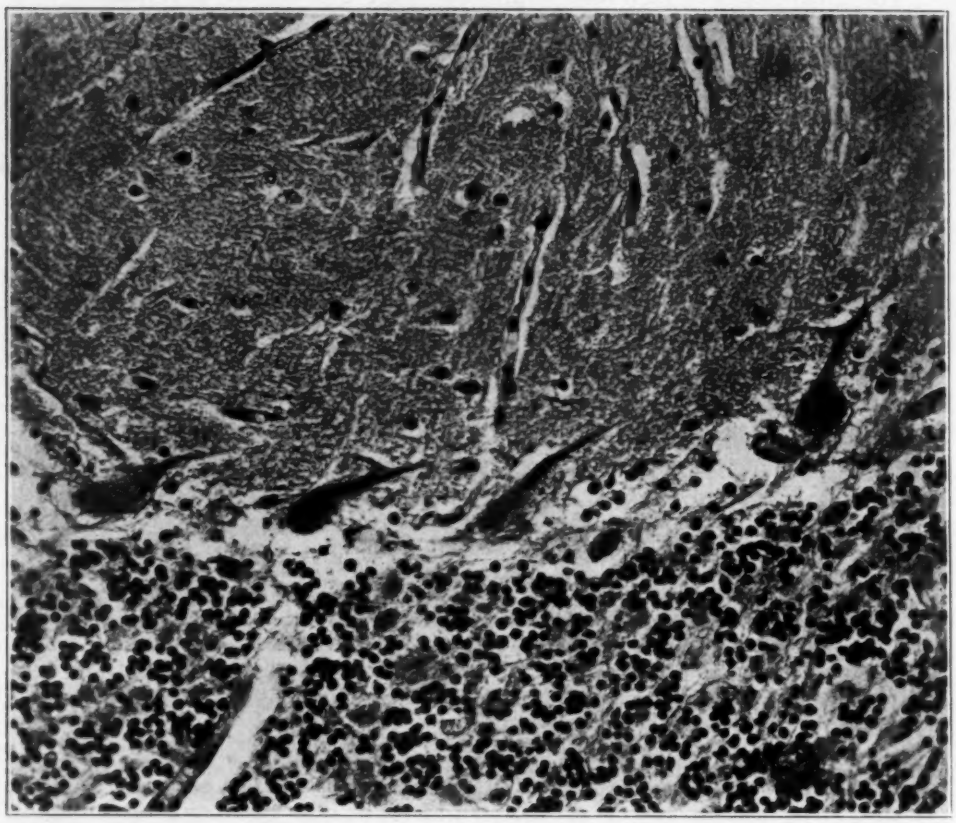

Fig. 1 (case 1).—Necrosis of remaining Purkinje cells following heat stroke (courtesy of United States Army Medical Museum, acc. no. 69622); × 285.

particularly notable in the meninges. The ganglion cells and Purkinje cells of the cerebellum showed disintegration of Nissl bodies, in proportion to the period of exposure. These changes were demonstrable as early as three hours after exposure, while the ventral horn cells were less intensely involved. Schwab also noted that postmortem studies on patients who died of sunstroke showed petechiae and smaller or larger ecchymoses of the serous membranes, and sometimes of the meninges and various parts of the nervous system. He also noted disintegration of Nissl bodies. In his review, he cited a case reported by A. Cramer, in 1890, in

2. Schwab, W.: Brain Changes in Sunstroke, J. A. M. A. **84**:712 (Feb. 28) 1925.

which the patient died three months after insolation, during which period severe mental disturbances were present. Autopsy revealed extensive atrophy of the cortical fibers of the cerebrum and the cerebellum alike, while the ganglion cells were intact. Schwab's own case was that of a man aged 25 who died two days after being stricken. Autopsy showed that the convolutions were flattened and the surface of the brain extremely dry. The entire medullary substance was filled with scattered petechiae, most numerous at the level of the corpus callosum. The cortical substance showed disintegration of Nissl bodies but no neuronophagia.

In 1937, Hartman [3] reported a case and the results of experimental work in this field. His patient, a white man aged 31, had been given fever therapy for bilateral iridocyclitis. The first six treatments, given at five to seven day intervals, were each of five hours' duration, and the temperature ranged from 103 to 107.4 F. After this series, treatments were discontinued for about six months and then resumed. The patient received six similar treatments, with no untoward effects. Immediately after the seventh treatment he went into shock and died twenty hours later. The height of the temperature during fever was not reported. Autopsy revealed that the right lobe of the cerebellum was a soft, hemorrhagic, necrotic mass. Sections from the cerebrum showed marked edema, with unusually large clear spaces about the smaller vessels and about many of the pyramidal cells. The pyramidal cells themselves stained poorly. The nuclei were broken up, and Nissl bodies could not be made out. Sections from the better preserved, left lobe of the cerebellum showed considerable congestion and some diffuse hemorrhage. The Purkinje cells were poorly stained and the nuclei pyknotic. Tissue of the necrotic right lobe took a homogeneous pink stain, although nuclei here and there stained poorly. There was extensive hemorrhagic infiltration. No evidence of thrombosed blood vessels could be made out.

Hartman exposed 15 animals to high temperatures for definite periods. He stated:

> Constant and severe anoxia is shown by the decreased oxygen saturation of the arterial blood and the low oxygen content of the venous blood in animals after fever therapy. . . .
>
> Factors producing anoxia during fever therapy are alkalosis, accelerated blood flow, increased temperature of the blood and increased demand for oxygen in the tissues. The last results from the increased metabolism and the depressed utilization of oxygen of the tissues, especially the brain, were due to the histotoxic effect of the sedatives used.

In 1918 Stewart [4] reported a case of cerebellar syndrome following heat stroke. A soldier aged 32 was found unconscious after marching a mile (1.6 kilometers) in the sun, the temperature being 109 F. in the shade. His temperature remained high for six days, during which time he was comatose and incontinent and all deep reflexes were absent. Ten days after the onset of illness examination revealed exaggerated tendon reflexes; severe ataxia; incoordination of movements in the arms and legs; athetoid movements when he grasped objects; scanning, indistinct speech, and pronounced nystagmus. One year later the patient was described as hyperemotional, but well oriented and with good insight. He displayed notable incoordination and ataxia of the cerebellar type, marked dysmetria of all movements, asynergia, adiadokokinesis and cerebellar catalepsy.

In 1912 Weisenburg [5] reported a case of severe sunstroke followed by multiple nervous lesions, producing mania, convulsions and coma, followed by acute

3. Hartman, F. W.: Lesions of the Brain Following Fever Therapy, J. A. M. A. **109**:2116 (Dec. 25) 1937.

4. Stewart, R. M.: Occurrence of a Cerebellar Syndrome Following Heatstroke, Rev. Neurol. & Psychiat. **16**:78, 1918.

5. Weisenburg, T. H.: Nervous Symptoms Following Sunstroke, J. A. M. A. **58**:2015 (June 29) 1912.

cerebellar ataxia, loss of speech and spastic symptoms. The temperature, initially 107 F., did not become normal until twenty-two days later. In reviewing the literature up to this time, Weisenburg referred to 2 cases reported by Nonne, 1 in 1905 and 1 in 1907, in which acute ataxia followed overheating.

Case 2.—A white man aged 38, with chronic alcoholism, was admitted by ambulance to the Central Dispensary and Emergency Hospital, service of Dr. M. W. Perry and Dr. W. K. Myers, on Aug. 8, 1937. The axillary temperature was 108 F. and the pulse rate 160, and he had profuse watery diarrhea shortly after admission. He was immersed in ice water for twenty minutes and then wrapped in wet sheets and exposed to an electric fan. On admission to the ward one hour later his temperature was 100.8 F. by rectum. In the next twelve hours he received 3,000 cc. of isotonic solution of sodium chloride intravenously. When he became rational he gave the following story: The day before admission, while working out of doors at a temperature of 106 F., he felt ill. That night he drank three bottles of beer. The next day he stayed home, feeling unable to work. He took a large quantity of water but did not perspire. His mind was completely clear until he fell to the floor, after dinner.

After emergency measures were carried out, the temperature was 101 F., the pulse rate 86, the respiratory rate 20 and the blood pressure 140 systolic and 85 diastolic. There were severe nystagmus on any motion or attempt at fixation, thickness of speech, intention tremor

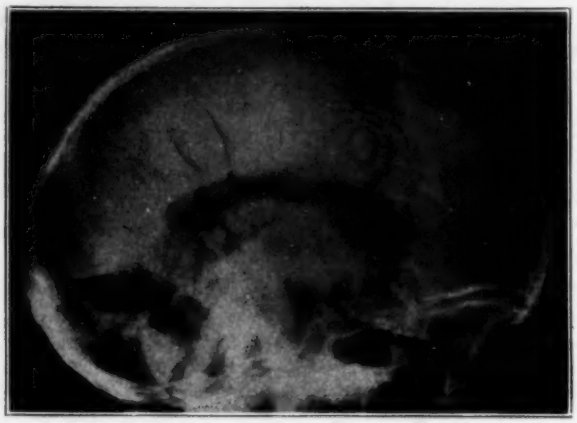

Fig. 2 (case 2).—Encephalogram, showing cerebellar atrophy following heat stroke.

and poor coordination of movement. No motor or sensory loss was apparent. His temperature remained elevated until August 22 (fourteen days) and then gradually fell to normal in the next five days. He was discharged from the hospital on September 14, with his neurologic status unchanged.

On Oct. 1, 1937 he was admitted to the psychopathic ward of Gallinger Municipal Hospital for mental observation. At this time the examiner made the following note: "The patient is lying in bed; he is unable to stand or to sit up in bed. He has a pronounced speech defect; frequently his production is utterly unintelligible. He is oriented in all fields. Incoordination is present in both upper and lower extremities. Tremor is accentuated on active motion."

Examination on November 19 showed notable incoordination on heel to shin and finger to nose tests and marked tremor, which was accentuated on movement. The deep reflexes in the upper extremities were increased. The examiner noted motor dyarthria, due to incoordination of the lips and tongue. The patient became stronger; his speech improved, and he was able to raise himself up in bed and to maintain himself in a chair for several hours. He was discharged on Nov. 22.

On April 15, 1940 he was admitted to the neurologic service of Gallinger Municipal Hospital, at which time examination revealed slow, aimless, purposeless movements of the arms and legs when the patient was talking; slurred speech; spastic, slapping gait, and complete incoordination. An encephalogram on April 17 showed a large collection of air overlying the cerebellum (fig. 2) and a conspicuously dilated fourth ventricle, but no other abnormality.

He was again received in the ward for patients with neurologic diseases of Gallinger Municipal Hospital, on Jan. 14, 1941. On this admission he could walk, but not without assistance, and he expressed a constant fear of falling. The neurologic status was little changed.

The patient was readmitted to Gallinger Municipal Hospital for follow-up studies on Oct. 15, 1942. At this time he added the information that in 1926 he had had a heat stroke, with vertigo, nausea and vomiting, and was bedridden for two days. At the time of the present admission his speech showed improvement. In spite of the Irish brogue and the dysarthria, it was not difficult to understand him. In the preceding year he had regained sensibility to light touch over the lower extremities. The senses of taste and smell were impaired after the stroke but had improved in the past year, so that he enjoyed smoking and could distinguish odors and flavors.

On the present admission he adjusted himself quickly to ward routine. He was able to get out of bed without assistance and, by holding on to the bed, could take the necessary step or two to reach the wheel chair, in which he spent most of his time. He had a fixed facial expression, but when he was spoken to he usually broke into an extremely broad grin, which

Fig. 3 (case 2).—Cerebellar ataxia and grimacing shown by patient in attempting to grasp a fountain pen.

Fig. 4 (case 2).—Signature of the patient.

accentuated the droop of the right corner of the mouth and the ptosis of the right lower eyelid. When he talked there were notable slapping of the tongue and incoordinate twisting of the lips, together with purposeless, slow, somewhat athetoid movements of the hands. Dysmetria, ataxia and adiadokokinesis were all pronounced and equal on the two sides (fig. 3). Hypotonicity was not remarkable except in the hands. No pathologic reflexes were elicited. Sensory perception was normal in all fields. He could stand unassisted for only a few seconds at a time, with the feet very wide apart and the trunk tending to lean forward from the hips. There was notable incoordination in gait, the trunk lurching first backward and then forward; the legs, flexed at the hips and remaining in extension at the knee, were lifted high and slapped forcibly to the ground. His handwriting was large and childlike, but he was proud of his ability to write his name (fig. 4). No nystagmus was noted during this admission. Psychometric examination revealed that his intelligence was superior to that of the average unskilled laborer, the intelligence quotient being 94. Memory was good; reasoning ability and judgment were unimpaired, and his ability to think in abstract terms was equal to that of the average adult.

CONCLUSION

A patient who had survived a period of extreme hyperthermia of about fourteen days presented the signs of cerebellar syndrome within forty-eight hours after the onset of illness. Cerebellar degeneration was observed post mortem in another patient who died after about twenty hours of hyperpyrexia associated with sunstroke. We believe that the most permanent and significant pathologic change in cases of cerebellar syndrome following hyperpyrexia is destruction of the Purkinje cells of the cerebellar cortex.

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CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE

II. MENTAL DEFICIENCY

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Previous observations on patients with mental deficiencies include studies of cerebral arteriovenous oxygen differences associated with mongolism,[1] cretinism,[2] phenylpyruvic oligophrenia [1] and undifferentiated mental deficiency.[3] The purpose of the present communication is to extend these observations to patients with amaurotic familial idiocy, hydrocephalus and microcephaly. The combined data present the opportunity for comparison of the cerebral arteriovenous oxygen differences associated with the various types of mental deficiency. The methods for the collection and analysis of the cerebral arterial and venous blood are the same as those described in part I of this series.[3]

RESULTS

Amaurotic Familial Idiocy.—Eleven observations on the cerebral arteriovenous oxygen differences for the 3 patients with amaurotic familial idiocy, between 1 to 1½ years of age, are presented in table 1. The average for 6 observations in which

TABLE 1.—*Cerebral Arteriovenous Oxygen Differences in Patients with Amaurotic Familial Idiocy for Cerebral Blood from Internal Jugular Vein and from the Fontanel*

	Internal Jugular Vein, Vol. per Cent	Fontanel, Vol. per Cent
	6.4	7.3
	5.7	7.4
	6.2	7.7
	5.8	6.6
	4.3	8.6
	5.8	
Average	5.7	7.5

the arterial blood was compared with the internal jugular venous blood was 5.7 volumes per cent, and the average for 5 observations made by comparison of arterial blood with blood from the fontanel was 7.5 volumes per cent. The values for the cerebral arteriovenous oxygen differences for the children with amaurotic familial idiocy were closer to those for the newborn (8.6 volumes per cent [3]) than they were to children of their own age. The values obtained for the children with amaurotic familial idiocy may be compared with the average value of 3.4 volumes

This study was aided by a grant from the John and Mary R. Markle Foundation.

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1. Himwich, H. E., and Fazekas, J. F.: Cerebral Metabolism in Mongolian Idiocy and Phenylpyruvic Oligophrenia, Arch. Neurol. & Psychiat. **44**:1213 (Dec.) 1940.

2. Himwich, H. E.; Daly, C.; Fazekas, J. F., and Herrlich, H. C.: Effect of Thyroid Medication on Brain Metabolism of Cretins, Am. J. Psychiat. **98**:489, 1942.

3. Himwich, H. E., and Fazekas, J. F.: Cerebral Arteriovenous Oxygen Difference: I. The Effect of Age and Mental Deficiency, Arch. Neurol. & Psychiat. **50**:546 (Nov.) 1943.

per cent for 12 observations on children with mongolism 3 months to 5 years of age, and with the average value of 4.7 volumes per cent for 5 children with moderately severe hydrocephalus, from ½ year to 5 years of age.

Hydrocephalus and Microcephaly.—In only 1 of 6 patients with hydrocephalus was the arteriovenous oxygen difference significantly reduced (table 2) when age was taken into consideration (compare with table and figure of part I [3]). For that patient the cerebral arteriovenous oxygen difference was 2.2 volumes per cent in an observation made one day before the brain ruptured. Autopsy revealed that the thickness of the remaining cerebral cortex was reduced to 2 mm. For the 5 other patients with hydrocephalus the differences were what might have been expected at their ages. We have 4 observations on patients with primary microcephaly (table 2), i. e., with no apparent cause for the small size of the cranium

TABLE 2.—*Cerebral Arteriovenous Oxygen Differences for Children with Hydrocephalus and Microcephaly*

Hydrocephalus		Microcephaly	
Age	Arteriovenous Oxygen Difference, Vol. per Cent	Age	Arteriovenous Oxygen Difference, Vol. per Cent
Less than 1 year	2.2	5 years	4.1
Less than 1 year	4.6	8 years	3.1
Less than 1 year	4.8	15 years	6.2
3 years	4.4	22 years	6.5
5 years	3.8		
5 years	5.7		

TABLE 3.—*Average Cerebral Arteriovenous Oxygen Differences for Adults 20 Years of Age or Older*

Condition	Arteriovenous Oxygen Difference, Vol. per Cent
Normal	6.7 (96)*
Undifferentiated mental deficiency	6.6 (45)
Mongolism	5.6 (30)
Cretinism	5.5 (17)
Phenylpyruvic oligophrenia	5.5 (9)

* Numbers in parentheses indicate the number of observations from which the average values were obtained.

except insufficient growth of the brain. Their arteriovenous oxygen differences fell within normal limits for their ages.

Mongolism, Cretinism and Phenylpyruvic Oligophrenia.—In the first study [3] it was concluded that patients with undifferentiated mental deficiency possess cerebral arteriovenous oxygen differences like those of normal persons, and probably have a normal cerebral metabolic rate. In order to make easier comparisons with data previously obtained results for persons with mongolism, cretinism and phenylpyruvic oligophrenia have been reanalyzed on an age basis (table 3), similar to that of the patients with undifferentiated mental deficiency. Only in one age group, that of persons 20 years and more, were there sufficient data to justify comparison of all three types of mental deficiency. The average value of 6.6 volumes per cent for persons with undifferentiated mental deficiency was higher than the values for patients with mongolism, cretinism or phenylpyruvic oligophrenia. The average cerebral arteriovenous oxygen difference for 30 patients with mongolism between the ages of 20 and 45 was 5.6 volumes per cent. It was possible to study only 9 patients, between 20 and 37 years of age, with the rare disease of phenyl-

pyruvic oligophrenia. Their average cerebral arteriovenous oxygen difference was 5.5 volumes per cent. Reexamination of data previously presented on cretins revealed an average of 5.5 volumes per cent. Even though this is an average for only 6 persons, between the ages of 22 and 31, each subject, nevertheless, was examined more than once, on different days, and the average was that of 17 observations. When the Fisher *t* test was applied,[4] the differences between the values for persons with undifferentiated mental deficiency and the values for persons with mongolism and cretinism were significant, and the differences between the values for persons with undifferentiated mental deficiency and the values for persons with phenylpyruvic oligophrenia were probably significant. Data on persons with mongolism are available for a comparison of the effects of age on the cerebral arterio-

TABLE 4.—*Average Cerebral Arteriovenous Oxygen Differences for Persons with Mongolism or Undifferentiated Mental Deficiency*

Age, Yr.	Undifferentiated Mental Deficiency	Mongolism
Less than 10	4.7 (30)*	4.4 (21)
10 to 19	5.4 (55)	5.9 (17)
20 and over	6.6 (45)	5.6 (30)

* Numbers in parentheses indicate the number of observations from which the average values were obtained.

TABLE 5.—*Cerebral Arteriovenous Oxygen Differences for Persons with Various Forms of Mental Deficiency* *

Condition	Age, Yr.	No. of Observations	Average Cerebral Arteriovenous Oxygen Differences	Cerebral Metabolic Rate
Undifferentiated mental deficiency	20-55	45	6.6	Normal
Hydrocephalus, not terminal	Less than 1 to 5	5	Normal	Reduced
Microcephaly	5-22	4	Normal	Reduced
Mongolism	Less than 10	21	4.4	Reduced
	10-19	17	5.9	Reduced
	20 and over	30	5.6	Reduced
Cretinism	Over 20	17	5.5	Reduced
Phenylpyruvic oligophrenia	Over 20	9	5.5	Reduced
Hydrocephalus, terminal	Less than 1	1	2.2	Reduced
			Internal Jugular Vein	
Amaurotic familial idiocy	1-1½	6	5.7	
			Fontanel	
	1-1½	5	7.5	

* The values for cerebral arteriovenous oxygen differences are based on observations; the cerebral metabolic rates are estimated.

venous oxygen difference with the values for persons with undifferentiated mental deficiency. It is significant that the general pattern is the same as that for persons with undifferentiated mental deficiency, namely, one of increasing cerebral arteriovenous oxygen differences as age advances. There is, however, an important modification. Table 4 shows that the cerebral arteriovenous oxygen differences for persons with mongolism rise from the first to the second decade and then remain the same until old age. The increase in the cerebral arteriovenous oxygen difference, therefore, ceases ten years earlier for the patient with mongolism than for the patient with undifferentiated mental deficiency. Presumably, the increase in cerebral metabolism also stops at the earlier age. The data on the cerebral arteriovenous oxygen differences and on the cerebral metabolic rate are summarized in table 5.

4. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, 1928.

COMMENT

Amaurotic Familial Idiocy.—The arteriovenous oxygen difference which we have observed in patients with this condition was relatively high—higher than the values for patients with mongolism and hydrocephalus of approximately the same ages (tables 2 and 5). As we have stated, the children with familial idiocy were between the ages of 1 and 1½ years, and since we have no control experiments on normal babies between these ages, we could not say whether or not the values for the babies with familial idiocy deviated from the normal. We do suspect, however, that the children with amaurotic familial idiocy had a higher arteriovenous oxygen difference than normal, and from certain morphologic evidence [5] we believe that, despite this high oxygen difference, their metabolic rate was depressed. In this instance there appears to be no correlation between the arteriovenous oxygen difference and the cerebral metabolic rate; at least, no such claim can be made until further work is done along this line.

In the meantime, our belief that a child with amaurotic familial idiocy suffers from a depressed cerebral metabolic rate may be supported by certain biochemical and morphologic evidence. Here we find that the actively respiring gray matter is supplanted by a lipid material, substance X of Klenk,[6] which is probably relatively inert from the respiratory standpoint. It is well known that the metabolic rate of gray matter is much higher than that of white matter, presumably because of a higher concentration of respiratory enzymes in the former.[5d] The distribution of the lipid matter in the brain in a case of amaurotic familial idiocy may explain the reason for the smaller arteriovenous difference for blood drawn from the internal jugular vein than for that collected from the fontanel. According to Hassin,[5a] though the abnormal accumulation of lipids may occur diffusely throughout the entire central nervous system, it is especially obvious in the optic thalamus. Such a differential distribution of pathologic changes may account for a lower utilization of oxygen in the blood collected from the internal jugular vein, which represents the return flow from the entire organ, including the optic thalamus, than from the fontanel, which contains the venous blood coming chiefly from the cerebral hemispheres.

Hydrocephalus.—The low oxygen consumption of the patient who died with extreme hydrocephalus must be regarded as a result of destruction of brain tissue and as indicative of an impaired cerebral metabolic rate. Unless such destruction is extensive, however, no decrease of the cerebral arteriovenous oxygen difference is observed, a condition presented by the 5 other patients with hydrocephalus. If these 5 patients had a depressed cerebral metabolism, the cerebral blood flow must have slowed to maintain the arteriovenous oxygen difference.

Microcephaly.—If the usual relationship existed between the cerebral arteriovenous oxygen difference and the cerebral blood flow in the patients with microcephaly, their cerebral metabolic rate per gram of brain was not depressed. Because of the reduction of cerebral tissue, however, the total metabolism of the brain may have been less than normal.

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5. (*a*) Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, Philadelphia, William Wood & Company, 1933, p. 315. (*b*) Klenk, E.: Ueber die Natur der Phosphatide der Milz bei der Niemann-Pickschen Krankheit, Ztschr. f. physiol. Chem. **229**:151, 1934; (*c*) Ueber die Natur der Phosphatide und anderer Lipoide des Gehirns und der Leber bei der Niemann-Pickschen Krankheit, ibid. **235**:24, 1935. (*d*) Holmes, E. G.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

6. Klenk (footnote 5 *b* and *c*).

Mongolism, Cretinism and Phenylpyruvic Oligophrenia.—There is no reason to suspect an accelerated cerebral blood flow in the patients with mongolism, cretinism or phenylpyruvic oligophrenia, and it may even have been reduced in association with the first two diseases. If the cerebral blood flow was either normal or slow in all patients with these disorders, then the diminished arteriovenous oxygen differences indicate a subnormal cerebral metabolic rate. In these three groups of patients the mental deficiency was probably associated with an inadequate elaboration of cerebral energy.

The low cerebral metabolism of the patients with mongolism may be explained by degenerative processes in the cerebral gray matter. Morphologic studies revealed that such persons exhibit degeneration of brain tissue, loss of nerve cells and atrophy of the cortex.[7] These differences between persons with mongolism and normal persons are most pronounced after 19 years of age as indicated by failure of the cerebral arteriovenous oxygen difference to rise after that period. The increase in concentration of cerebral enzymes which occurs as growth proceeds is arrested ten years earlier in the person with mongolism than in the normal person. Evidence presented by Benda [7b] is in agreement with this conclusion of the early arrest in growth and development of the brain in association with mongolism.

In cretins, as in mongolism, a low cerebral metabolic rate may be attributed to an inadequate development of cerebral enzymes. It is thought that thyroxin stimulates the metabolic rate by increasing the concentration of enzymes, an effect exerted directly on the protein moiety of the enzyme.[8] In athyrotic cretins the subnormal cerebral metabolism may therefore be ascribed to a diminished concentration of respiratory enzymes. The cause of the depression of cerebral metabolism in patients with phenylpyruvic oligophrenia is unknown. It is recognized, however, that such patients lack the enzyme necessary for the oxidation of phenylalanine.

CONCLUSIONS

The cerebral arteriovenous oxygen differences are high in patients with amaurotic familial idiocy and normal for those with microcephaly and hydrocephalus not in the terminal stages.

Above the age of 20 years the cerebral arteriovenous oxygen difference is lower for patients with mongolism, cretinism and phenylpyruvic oligophrenia than for persons with undifferentiated mental deficiency.

In persons with mongolism the cerebral arteriovenous oxygen difference ceases increasing ten years earlier than in those with undifferentiated mental deficiency.

It is suggested that cerebral metabolism is reduced in patients with mongolism, cretinism, phenylpyruvic oligophrenia, advanced hydrocephalus, microcephaly and amaurotic familial idiocy.

Albany Medical College.

7. (*a*) Meyer, A., and Jones, T. B.: Histological Changes in the Brain in Mongolism, J. Ment. Sc. **85**:206, 1939. (*b*) Benda, C. E.: The Central Nervous System in Mongolism, Am. J. Ment. Deficiency **45**:42, 1940. (*c*) Holmes.[5d]

8. Klein, J. R.: Nature of the Increase in Activity of the D-Amino Acid Oxidase of Rat Liver Produced by Thyroid Feeding, J. Biol. Chem. **131**:139, 1939.

CEREBRAL CORTEX OF A MAN WITH SENILE DEMENTIA BELIEVED TO BE 107 YEARS OLD[1]

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Among the numerous publications dealing with the morphologic and histologic characteristics of the senile brain there are a few scattered cases of very old brains (Simchowicz,[2] Gellerstedt[3] and others). The study of these specimens, however, was included as part of a more general investigation of old brains, without particular attention to the detailed consideration of the very old brain. The results of the present studies corroborated the general observations that have been made on old brains. As far as we know, there are only 2 specimens of brains (Kuczynski[4] and Aksel[5]) obtained from persons more than 100 years of age on which such monographic studies, based on appropriate methods,[6] have been made. None of the aforementioned reports, however, deals with the problems of cortical organization which we shall consider in this study. In accordance with the more or less predominant cell type in a given area, von Economo and Koskinas[7] distinguished areas of pyramidization, granularization and spindlization. These three types of cortical organization characterized the adult brain. Little is known about their formation in the course of cortical development. In general, the embryonic and the infantile brain is richer in "granular" cells than the adult brain. From the viewpoint of

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1. It is true that the statement of the patient could not be verified objectively, but this holds true for the very small number of cases of persons over 100 years of age submitted to a systematic study by previous authors. We feel that there is no obvious reason to doubt the patient's own statement, his psychiatric picture at the time he made his statement suggesting no depersonalization or any evidence of delusions or disorientation with regard to his own person. But even if this were true, he would still have been a very old man, and the neuropathologic observations would still have to be interpreted as those pertaining to a very old brain. The observations, therefore, would lose nothing of their value as first statements of their kind.

2. Simchowicz, T.: Histologische Studien über die senile Demenz, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über Grosshirnrinde, Jena, Gustav Fischer, 1910-1911, vol. 4, p. 267.

3. Gellerstedt, N.: Zur Kenntnis der Hirnveränderungen bei der normalen Altersinvolution, Uppsala, Almqvist & Wiksell, 1933.

4. Kuczynski, M. H.: Von den körperlichen Veränderungen bei höchstem Alter, Krankheitsforschung **1**:85-163, 1925.

5. Aksel, I. S.: Ueber das Gehirn des "ältesten Mannes der Welt" (Zaro Aga), Arch. f. Psychiat. **106**:260-266, 1937.

6. For general bibliography concerning very old brains, see: Critchley, M.: Ageing of the Nervous System, in Cowdry, E. V.: Problems of Ageing, Baltimore, Williams & Wilkins Company, 1939, pp. 483-500.

7. von Economo, C., and Koskinas, G. N.: Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen, Berlin, Julius Springer, 1925.

comparative neurology it is noticeable that, according to Abbie,[8] granularization is already present in the monotreme cortex, whereas the same author could not detect pyramidization in this primitive mammalian species. One of us (W. R.)[9] observed all the three types of cortical organization in Macropus, a highly specialized marsupial (Diprotodontia). Nothing is known about the behavior of these types of cortical organization in old age and in very old age, no attention having been given to this problem by previous investigators.

REPORT OF A CASE

History.—J. H., an unmarried white man, was born in Ireland. He stated that he was 29 years of age two years before Lee's surrender, which would have made him 107 years of age at the time of his death on Nov. 3, 1941.

He came to this country at the age of 18 years; he worked as a farmhand and lived alone until his admission to the Eastern State Hospital, on Sept. 23, 1930. He was supported by the county prior to his commitment to the hospital, which was necessitated by his irritability, insomnia, wandering, loss of memory, silly conduct and suspiciousness.

During his residence at the hospital he was for the most part quiet and well behaved but occasionally became irritable and pugnacious. He exhibited characteristic symptoms of a psychosis of the organic reaction type and of senile deterioration, which was progressive, terminating in a bedridden, vegetative state.

Physical Examination.—The patient was of small stature, with pronounced dorsal kyphosis and scoliosis to the right. He was fairly well nourished. There was evidence of severe peripheral arteriosclerosis. The heart and lungs were normal. The blood pressure was 140 systolic and 90 diastolic. There was slight generalized tremor, which became more noticeable on occasions. The left pupil was once recorded as being smaller than the right; it reacted sluggishly to light and in accommodation. Neurologic examination otherwise revealed nothing abnormal. The patient became progressively weaker physically and was bedridden for about one month before his death.

Postmortem Examination.—General Gross Observations: The subject was fairly well nourished and did not appear to be over 60 years of age. The lungs weighed 360 Gm. each and showed a few scattered healed, calcified tuberculous lesions and a small cavity measuring 2 cm. in diameter in the apex of the left lung. The weight of the heart was 320 Gm. There were a fibrous epicardial plaque on the anterior wall of the right ventricle and moderate fibrosis of the myocardium. The mitral leaflets showed calcification, with partial stenosis. The aortic leaflets were slightly thickened. The coronary vessels showed considerable tortuosity, with moderate arteriosclerotic changes but no occlusion. The first portion of the aorta was free from atheromatous changes, but the transverse, thoracic and abdominal portions showed severe arteriosclerotic changes, with calcification and ulceration. The liver was small, weighed 980 Gm. and had a dark brownish, mottled appearance. The gallbladder was normal. The spleen weighed 80 Gm., and the pulp was semisolid. The pancreas and the adrenals were normal. The right and left kidneys weighed 100 and 85 Gm. respectively. The capsules stripped with slight difficulty, a diffusely granular surface with many small surface cysts remaining. The renal architecture was disturbed; the cortical striations were indistinct. The bladder, the prostate and the testicles were normal. There was a small hydrocele on the right. The esophagus, the stomach and the small intestine were normal. The mucosa of the cecum and colon showed what appeared to be small, superficial areas of ulceration. The sigmoid and rectum appeared normal.

Microscopic Examination of the Organs (Dr. M. L. Dreyfus, Clifton Forge, Va.): The gross pathologic observations were confirmed by the microscopic studies, which revealed the following changes: interstitial fibrosis of the myocardium; fibrous thickening of the epicardium; arteriosclerosis of the aorta; arteriosclerosis of the kidneys; fibrocaseous pulmonary tuberculosis; chronic pulmonary emphysema; functioning testicles (complete spermato-

8. Abbie, A. A.: Cortical Lamination in the Monotremata, J. Comp. Neurol. **72**:429-467, 1940; The Excitable Cortex in Parameles, Sarcophilus, Dasyurus, Trichosurus and Wallabia (Macropus), ibid. **72**:469-487, 1940; Cortical Lamination in a Polyprotodent Marsupial, Perameles Nasuta, ibid. **76**:509-536, 1942.

9. Riese, W.: The Cellular Structure of the Marsupialian Cortex, Naturaliste canad., to be published.

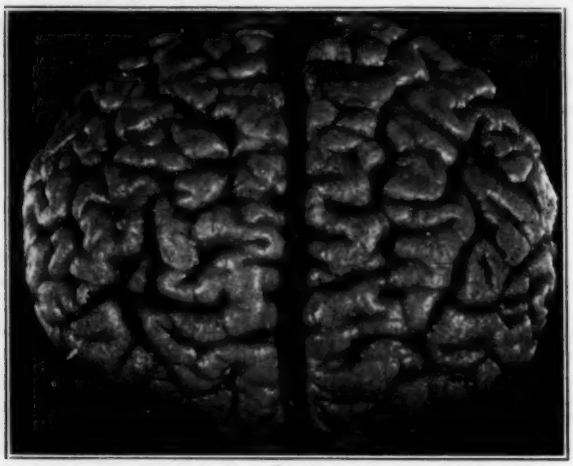

Fig. 1.—Frontal lobes of the brain, showing slight convolutional atrophy.

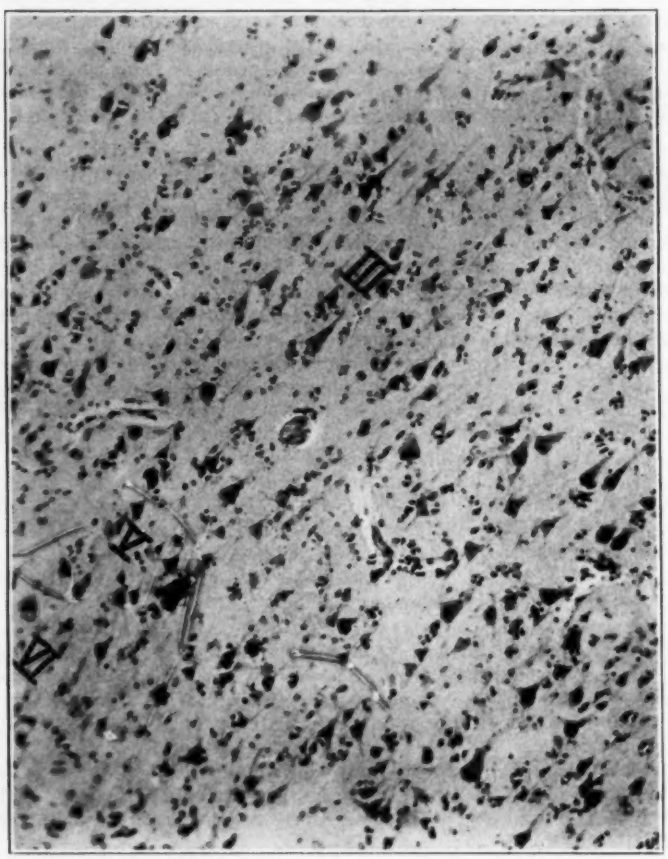

Fig. 2.—Area FA of von Economo, showing pyramidization; × 190.

genesis); brown atrophy of and fatty changes in the liver, and atrophy of the spleen. No signs of regeneration were noted in any of the organs. The normal, as well as the abnormal, observations did not differ from what may be noted in any elderly person, but the complete spermatogenesis was remarkable.

Gross Examination of the Brain: The brain weighed 1,280 Gm. The vessels at the base showed moderate arteriosclerotic changes. There was slight convolutional atrophy, limited to the anterior regions of the frontal lobe (fig. 1). Coronal sections through various levels of the brain revealed only slight internal hydrocephalus. No other gross neuropathologic changes were seen.

Histologic Examination of the Brain: The following areas of the cortex were examined: FA, FB, FE, TC, PB, PC, OC, LA, HD and IB.[10] In all these areas the general cytoarchitecture was well preserved, and the various regional variations of the cortical lamination

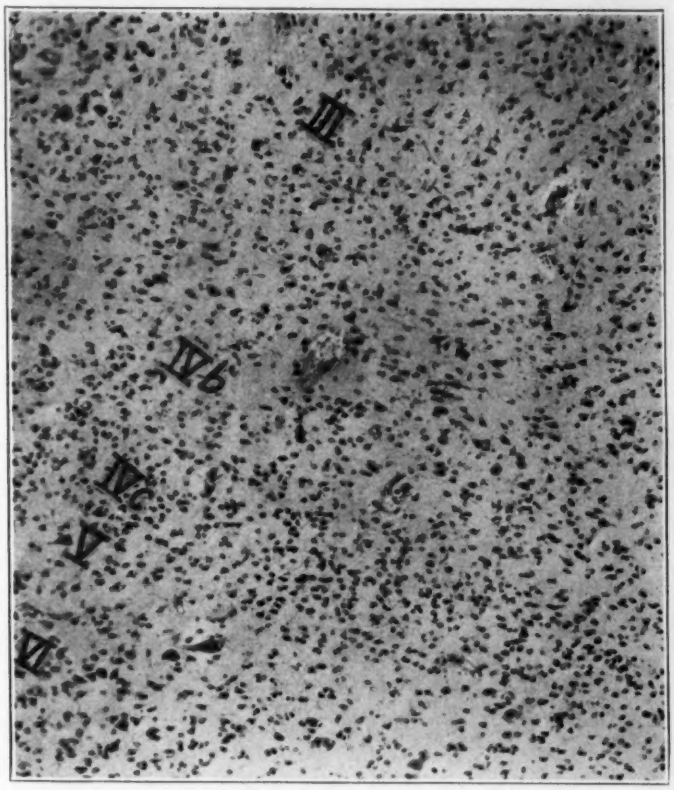

Fig. 3.—Area OC of von Economo, showing granularization; × 190.

could easily be identified. The same held true for the various types of cells. Definite pyramidization was to be seen in area FA, granularization in areas OC and TC and spindlization in area LA (figs. 2, 3 and 4). Thus, the structural characters of the cortex, its regional variations, as well as the three processes of pyramidization, granularization and spindlization, had undergone no change in this very old brain. The brain showed all the characteristics of a senile brain: cellular changes, gliosis, neurofibrillary alterations (Alzheimer type) and senile plaques (neurofibrillary changes and senile plaques however, were lacking in the cerebellar cortex). The cellular changes were of only moderate degree, and they did not lead to complete destruction or formation of so-called blanks in the cytoarchitectural picture. The cellular changes consisted of fatty degeneration, loss of distinct outlines, chromatolysis and increase

10. Terminology of von Economo and Koskinas.[7] The first letter in these designations indicates the lobe to which a given cortical area belongs.

in staining properties and eccentricity of the nucleus. These cellular changes seemed to be less pronounced in the koniocortex. However, the intensity of the cellular changes did not seem to be related to the size of the cell, the giant cells of the fifth layer of area FA being well preserved, whereas the large elements of the third, fourth and fifth layers of area OC were, in their turn, particularly involved. The glial reaction was intense. It consisted of so-called neuronophagia (involving not only the deep but the middle layers and in some instances —area FA—the whole section), perivascular gliosis, formation of glial symplasms and glial turfs. This glial reaction was much more pronounced in the areas of pyramidization than in those of granularization and spindlization. Only a small amount of intracellular pigment was noted. There was intense and generalized proliferation of the vessels throughout the white

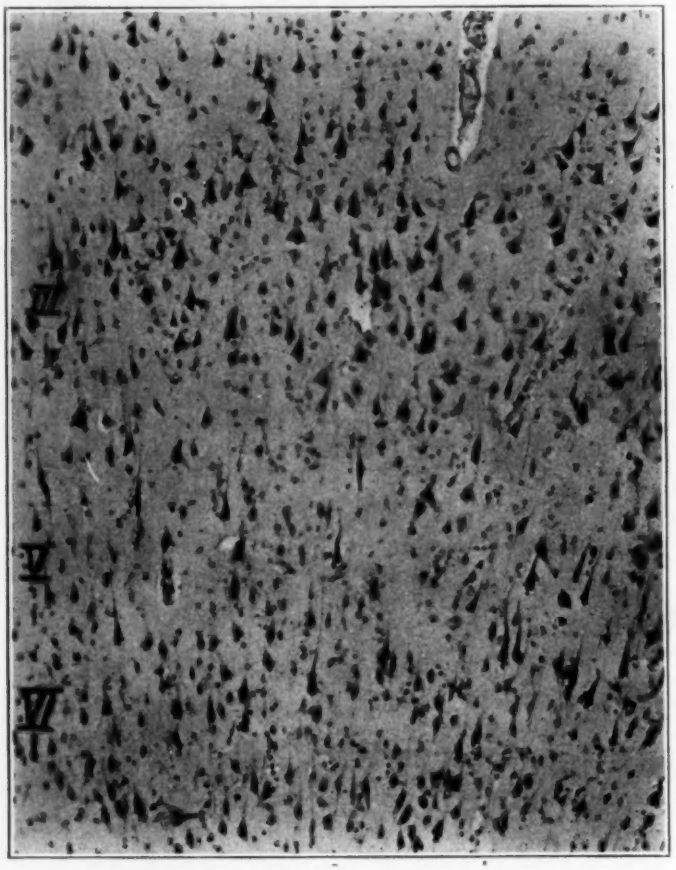

Fig. 4.—Area LA of von Economo, showing spindlization; × 190.

matter, which showed a cribriform state. There were also thickening and hyaline degeneration of the capillary wall and capillary fibrosis. Binucleated ganglion cells were noted in areas FA, FB and LA. Microscopic areas of softening were seen in areas OC and LA; they revealed an excellent glial and mesenchymal organization. There was disseminated demyelination in the white matter of all cortical areas and in the cerebellum. *Plaques fibromyéliniques* could be seen in area FA and in the cerebellar cortex.

COMMENT

This very old brain was remarkable for the minimal degree of cortical (frontal) atrophy. Similar observations have been made by previous investigators on senile

brains (Grünthal,[11] Gellerstedt,[3] Aksel[5] and Rothschild[12]). The brain of a 107 year old man described here showed the well known histopathologic changes observed in senile persons irrespective of the presence of senile dementia. The cellular changes, however, could be considered only as moderate, and this is interesting not only because of the advanced age of the patient but because of the existence of a clinical picture of senile dementia for eleven years. The cytoarchitecture was intact and revealed the typical regional variations in all their integrity. Furthermore, the three processes of pyramidization, granularization and spindlization were obvious. The same held true for an 87 and a 91 year old brain studied recently by us, and this answers for the first time (and in a negative way) the question submitted by von Economo and Koskinas as to the possible change of the cytoarchitectural pattern in function of old age. Finally, this very old brain showed also a notable tendency to repair (mesenchymal and glial), and even regeneration (if such was the significance of binucleated ganglion cells and *plaques fibromyéliniques*). In this connection, it might be interesting to recall that Kuczynski,[4] observed typical signs of regeneration in the liver and pancreas of a man over 100 years of age. Further studies will have to show whether the regional variations in the degree of cellular changes and glial repair, both of which were much more striking in the areas of pyramidization than in the areas of granularization and spindlization, were merely individual features of this very old brain. Although previous investigators (Gellerstedt[3] and others) could not discover any constant areal variations in the intensity of cellular changes in senile brains, more notable cellular changes in area FA were also observed by us in the aforementioned brains of persons aged 87 and 91 years. This problem requires further investigation. In general, the very old brain reveals signs not only of disintegration but of new integration, and this may be a neurologic contribution to a revision of the traditional conception of old age.

SUMMARY

1. The cytoarchitecture in this very old brain was well preserved and revealed the well known regional variations.

2. There were definite pyramidization, granularization and spindlization.

3. The gross and histopathologic changes generally considered as characteristic of the senile brain were present to only a moderate degree.

4. Processes of repair and regeneration were detectable.

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11. Grünthal, E.: Die pathologische Anatomie der senilen Demenz und der Alzheimerschen Krankheit, in Bumke, O., and Förster, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, pp. 638-672.

12. Rothschild, D.: Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**:757-788, 1937.

Clinical, Technical and Occasional Notes

SENSORY RECEPTION IN HYSTERICAL ANESTHESIA AS MEASURED BY THE COLD PRESSOR RESPONSE

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The paradox of hysterical anesthesia consists of failure to perceive sensory stimuli despite intact and functioning innervation. The preservation of deep and superficial reflexes and the nonanatomic distribution of the anesthesia furnish evidence of the neurologic integrity of the affected parts. The psychodynamic features reveal the conversion nature of the symptoms.

The cold pressor test consists of a standard cold stimulus applied to an extremity as a procedure for quantitative estimation of the reactivity of the vasomotor system.[1] The response consists of an increase in systemic blood pressure on immersion of a limb in cold water. It has been demonstrated previously that the cold pressor response depends on the transmission of sensation through intact peripheral nerves.[2]

This study was undertaken to determine whether conscious perception of the stimulus is necessary to cause an elevation of blood pressure, or whether the reaction is the result of reflexes mediated at a lower level of integration.

METHOD

With the patient in a sitting position, the basal blood pressure is established after five or six readings. One extremity is then immersed in ice cold water for exactly one minute. It is usually possible to take three or four readings during the period of immersion. The normal response consists of elevation of the systolic and diastolic pressures, which may vary considerably but always occurs in the presence of intact innervation. There is a return to the basal level in a minute or two after withdrawal of the limb. The procedure is repeated on the opposite limb. Either the normal or the anesthetized limb may be used first without alteration of the results.

CASE MATERIAL [3]

Three patients with complete hysterical anesthesia of a foot, and 1 patient with anesthesia of one hand were studied. The part immersed was insensible to pain or cold. No discomfort or inclination to withdrawal was demonstrated while the anesthetic limb was being tested, and this was sharply in contrast to the emotional display when the contralateral extremity was immersed.

SUMMARY AND CONCLUSIONS

Four patients with a hysterically anesthetized limb showed a cold pressor response in the affected limb despite the denial of subjective sensations of pain or cold.

The cold pressor response of the affected limb was in all subjects similar to that of the normal limb.

Subjective perception of pain and cold is not necessary for completion of the cold pressor response.

From the Neuropsychiatric Section of the Thirty-Third General Hospital, Fort Jackson, S. C.

1. Hines, E. A., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions, Proc. Staff Meet., Mayo Clin. **7**:322-335 (June 8) 1932.

2. Sullivan, J. D.: Dependence of the Cold Pressor Reaction on Peripheral Sensation, J. A. M. A. **117**:1090-1091 (Sept. 27) 1941.

3. The first 2 patients were studied at the Station Hospital at Fort Eustis, Va., in October 1942; the other 2 patients were in the neuropsychiatric service of the Station Hospital, Fort Jackson, S. C., in January 1943.

Further evidence indicates that hysterical anesthesia does not block sensory stimuli at the lowest segmental levels.

These observations suggest that the cold pressor response may be useful in differentiation of hysterical and peripheral nerve anesthesias.

CASE 1.—K. R. had hysterical monoplegia with anesthesia of the right leg. The basal blood pressure was 118 systolic and 80 diastolic; the cold pressor response in the left leg was 128 systolic and 86 diastolic and in the right leg 124 systolic and 84 diastolic.

CASE 2.—A. A. had hysterical hemiplegia of the right side, with anesthesia of the right side of the face, the right arm and the right side of the trunk.

The basal blood pressure was 120 systolic and 90 diastolic; the cold pressor response on the left side was 130 systolic and 98 diastolic and on the right side 130 systolic and 98 diastolic.

CASE 3.—B. J. had hysterical palsy of the right leg, with rigidity and anesthesia.

The basal blood pressure was 130 systolic and 84 diastolic; the cold pressor response in the left leg was 140 systolic and 90 diastolic and in the right leg 145 systolic and 90 diastolic.

CASE 4.—C. O. had paralytic residuals of poliomyelitis, with hysterical anesthesia in the right leg.

The basal blood pressure was 132 systolic and 90 diastolic; the cold pressor response in the left leg was 140 systolic and 98 diastolic and in the right leg 150 systolic and 98 diastolic.

News and Comment

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Psychiatry.—By Examination: Helen Benczur, New York; Courtenay L. Bennett, Tampa, Fla.; Martin A. Berezin, Fort Meade, Md.; Leo Berman, Boston; Eric L. Berne, Brentwood, N. Y.; Nathan Blackman, Fort Leavenworth, Kan.; L. D. Borough, Fort Sill, Okla.; Lester L. Burtnick, Camp Carson, Colo.; John Melton Cotton, Jackson, Miss.; *Francis M. Forster, Philadelphia; Bernhardt S. Gottlieb, New York; John Edward Harty, Williamsburg, Va.; Elmer Haynes, Madison, Wis.; Margaret Hohenberg, New York; William T. Hyslop, Traverse City, Mich.; Mildred H. January, Hartford, Conn.; Henriette R. Klein, New York; Sidney D. Klow, Denver; Alan A. Lieberman, Elgin, Ill.; Elizabeth MacDougall, Winnetka, Ill.; James D. Mahoney, Norristown, Pa.; Johann Rudolf Marx, Ingleside, Neb.; *Charles I. Oller, Philadelphia; William L. Pious, Byberry, Philadelphia; *Theodore Rothman, Paterson, N. J.; Sidney Rubin, New York; Bertram Schaffner, Camp Gordon, Ga.; Lazarus Secunda, Indiantown Gap, Pa.; *Isaac Shapiro, Schenectady, N. Y.; Maurice D. Spottswood, Bethesda, Md.; Wolfgang M. F. Sulzbach, Waverly, Mass.; Morris J. Tissenbaum, Norwich, Conn.; Herbert A. Wiggers, New York, and Isadore Zfass, Carlisle, Pa.

On Record: Kilian K. Bluhm, New York; Edgar L. Braunlin, Dayton, Ohio; *Fred P. Currier, Grand Rapids, Mich.; Royal George Grossman, Camp Atterbury, Ind.; Samuel W. Hartwell, Snyder, N. Y.; George E. Hesner, New Orleans; Merrill Olmstead Parker, Auburn, N. Y., and Melvin John Rowe, Norwalk, Calif.

Neurology.—By Examination: *Louis S. Chase, Westover Field, Mass.; Joseph F. Dorsey, New Haven, Conn.; *Maurice H. Greenhill, Durham, N. C.; Solomon Lesse, Newport, R. I.; Richard L. Masland, Randolph Field, Texas; *Bernard C. Meyer, New York; *Bernard L. Pacella, New York; *Nathan N. Root, Brooklyn; *Sidney Rosenbliett, Westover Field, Mass.; *Siman Stone, Manchester, N. H.; *Ellsworth H. Trowbridge Jr., Camp Joseph T. Robinson, Ark., and *Carel van der Heide, Chicago.

On Record: Gabriel Steiner, Detroit.

Neurology and Psychiatry.—By Examination: Earl Hay Adams, New York; Andrew Russell Anderson, Atlanta, Ga.; Charles M. Holmes, Orangeburg, N. Y.; Heinz Lichtenstein, Buffalo; Else Pappenheim, New York; Eugene Pumpian-Mindlin, Fort McClellan, Ala.; Leo Rangell, Sheppard Field, Texas; Victor H. Rosen, Fort Jackson, S. C.; Gabriel A. Schwarz, Philadelphia; Isidor Silbermann, New York; John Edmund Skogland, New Orleans; Heyman Smolev, San Luis Obispo, Calif., and Samuel Yochelson, Camp Kilmer, N. J.

On Record: Andrew B. Jones, St. Louis, and Paul Loewy, New York.

* The asterisk denotes complementary certification.

DEPARTMENT OF PSYCHIATRY, McGILL UNIVERSITY

McGill University announces the creation of a department of psychiatry and, in association with the Royal Victoria Hospital, the establishment of an institute for research and teaching. Through the generosity of Sir Montagu and Lady Allan, a building and an extensive site have been provided.

The institute will contain fifty beds for patients suffering from early and acute psychiatric conditions. Facilities for intensive treatment are being set up. The development of research and treatment will be major objectives, and, with this in view, large and well equipped laboratories are to be provided.

The project is being supported both by the Rockefeller Foundation and the government of the Province of Quebec. Dr. D. Ewen Cameron has been appointed to the chair of psychiatry and will also be the director of the institute.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DEVELOPMENT OF THE HUMAN MESENCEPHALIC TRIGEMINAL ROOT AND RELATED NEURONS. WILLIAM F. WINDLE and JAMES E. FITZGERALD, J. Comp. Neurol. **77**:597 (Dec.) 1942.

Windle and Fitzgerald studied the brain stems of human embryos at the 4 to the 7 week stage and the brain stems of cat embryos at comparable stages. The material was prepared for fiber study. Motor and sensory roots of the trigeminal nerve began to develop during the fourth week of gestation. During the early part of the fifth week the sensory root fibers of the trigeminal nerve entered the metencephalon opposite the sulcus limitans. The ascending fascicles merged with the lateral longitudinal tract. This composite tract began at the isthmus and descended into the tegmentum of the myelencephalon. The motor root of the trigeminal nerve coursed through bundles of the lateral longitudinal tract medial to the sensory root. The mesencephalic root arose as part of the lateral longitudinal tract. Probst's tract arose in common with the mesencephalic root in the metencephalon. Its fibers could be differentiated from the mesencephalic root only by observing their origin from smaller, less argyrophilic, cells and their course caudal to the trigeminal nerve, where they lay medial to the spinal tact of the trigeminal nerve in the lateral longitudinal tract. ADDISON, Philadelphia.

THE NUMERICAL RELATION BETWEEN THE GANGLION CELLS OF THE RETINA AND THE FIBERS IN THE OPTIC NERVE OF THE DOG. L. B. AREY and M. GORE, J. Comp. Neurol. **77**:609 (Dec.) 1942.

Arey and Gore counted the ganglion cells in the retinas of 4 dogs, the sections having been stained with Ehrlich's hematoxylin, without a counterstain. The nerve fibers in 4 optic nerves were counted after the nerves had been treated with silver. The animals ranged in weight from 2.5 to 37 Kg. The number of ganglion cells in the retina varied from 149,320 to 192,160. The smallest retina had the greatest relative concentration of ganglion cells and vice versa. The total number of fibers in the optic nerve ranged from 152,360 to 164,920. The ratio of ganglion cells to nerve fibers was approximately 1:1. ADDISON, Philadelphia.

DEVELOPMENT OF THE CRANIAL SYMPATHETIC GANGLIA IN THE CAT. ELIZABETH J. COWGILL and WILLIAM F. WINDLE, J. Comp. Neurol. **77**:619 (Dec.) 1942.

Cowgill and Windle studied the development of the cranial sympathetic ganglia in 34 cat embryos. The embryos had a crown-rump length of from 3 or 4 to 60 mm. They were prepared by the pyridine-silver method. The cranial sympathetic ganglia are derived from neuroblasts which have migrated from the sensory ganglia of the fifth, seventh and ninth cranial nerves along nerve bundles. The ciliary ganglion was recognized at the 5.5 mm. stage as a distinct bud of cells protruding forward from the ophthalmic portion of the semilunar ganglion. At the 8 mm. stage a few cells had arrived at the site of the ganglion. The sphenopalatine ganglion was recognized at the 6 mm. stage by a migration of neuroblasts along the maxillary nerve. At the 7 mm. stage cells were seen to migrate from the geniculate ganglion along the greater superficial petrosal nerve. At the 11 mm. stage some cells had arrived at the site of the ganglion. The otic ganglion was recognized at the 7 mm. stage by a migration of cells from the semilunar ganglion along the mandibular nerve. At the 9 mm. stage migration was also occurring along the lesser superficial petrosal nerve. The earliest migration of the submaxillary ganglion was seen along the mandibular nerve at the 7 mm. stage. Migration was complete at the 15 mm. stage. ADDISON, Philadelphia.

THE NUMBER OF MYELINATED AND UNMYELINATED FIBERS IN THE OPTIC NERVE OF VERTEBRATES. S. R. BRUESCH and L. B. AREY, J. Comp. Neurol. **77**:631 (Dec.) 1942.

Bruesch and Arey determined the total fiber content of the optic nerves of thirty-three representative vertebrates. Portions of nerves from the same animal were treated with osmium tetroxide or with silver. All the fibers in hagfish and brook lamprey were unmyelinated. All

the fibers in the dogfish, shark pup, guitar fish, sting rat, shovel-nosed sturgeon, bowfin, goldfish, bullhead, duckling, chick, pigeon, dog, cat, rabbit, gray rat, guinea pig, sheep, macaque and man were myelinated. The opossum, bat and albino rat had respectively 33, 44 and 21 per cent of unmyelinated fibers.

ADDISON, Philadelphia.

SIZE, DEVELOPMENT AND INNERVATION OF LABYRINTH SENSORY AREAS IN SQUALUS. WILLIAM B. FREEDMAN and ROLAND WALKER, J. Comp. Neurol. **77**:667 (Dec.) 1942.

Freedman and Walker studied the size, development and innervation of the sensory area in the ears of a series of 22 dogfish. The approximate areas were determined by measurement and calculations from serially sectioned specimens. The sensory area was not sufficiently differentiated for measurement until the 48 mm. stage. In the 580 mm. specimen the sensory area, though immature, totaled 18 sq. mm. for one ear, as compared with 11 sq. mm. for the human ear. The total sensory area for one ear increased thirty times, while the body length increased twelve times.

FRASER, Philadelphia.

CYTOARCHITECTURE OF INDIVIDUAL PARIETAL AREAS IN THE MONKEY (MACACA MULATTA) AND THE DISTRIBUTION OF THE EFFERENT FIBERS. TALMAGE L. PEELE, J. Comp. Neurol. **77**:693 (Dec.) 1942.

Peele ablated individual parietal areas or areas 1, 2, 5 and 7 together in 9 young macaque monkeys, after demarcating the areas by electrical stimulation. The excised cortex was prepared for cell study. After three weeks the brains were removed. Blocks from each level of the spinal cord were prepared by the Marchi technic. The parietal cortex showed six well developed cell layers throughout, but the development of certain cell layers varied from one area to another. All the parietal areas sent association fibers to the adjacent cerebral lobes. All sent commissural fibers to the contralateral areas, to the homolateral pontile nuclei and to the thalamic nuclei—the lateralis posterior, the ventralis posterolateralis and the ventralis posteromedialis. Area 5 sent some fibers to the nucleus medialis dorsalis of the thalamus. All areas sent fibers through the pyramid to the spinal cord, where they accompanied the corticospinal tracts to the same and to the opposite side. Crossed fibers from all areas except 7 could be found at lumbar levels, but uncrossed fibers only from area 3 reached this level. Uncrossed fibers from other areas terminated at the cervical levels. Areas 3 and 5 sent fibers to the substantia nigra; areas 5 and 7, to the pretectal region, and area 7, to the superior colliculus.

ADDISON, Philadelphia.

TRANSYNAPTIC EFFECT OF NEONATAL AXON SECTION ON BOUTON APPEARANCE ABOUT SOMATIC MOTOR CELLS. MELVIN SCHADEWALD, J. Comp. Neurol. **77**:739 (Dec.) 1942.

Schadewald removed segments of the right sciatic and femoral nerves high in the thigh in a series of newborn kittens. In a second series the contents of the right orbit were removed. The animals were killed at the age of 21, 28, 60 or 90 days. The regions of the nuclei of the trochlear and abducens nerves and of the lumbosacral segments of the spinal cord of all animals were studied by means of silver impregnation. *Boutons terminaux* were not seen about the anterior horn cells in the newborn or in the young kittens. They were noted in the nuclei of the trochlear and abducens nerves at the postnatal age of 3 weeks and on the anterior horn cells of the lumbosacral segments of the spinal cord at the age of 4 weeks. Axonal section altered neither the time of appearance nor the number of *boutons* which appeared about somatic motor cells.

ADDISON, Philadelphia.

THE EARLY DEVELOPMENT OF THE MOTOR CELLS AND COLUMNS IN THE SPINAL CORD OF THE SHEEP. DONALD H. BARRON, J. Comp. Neurol. **78**:1 (Feb.) 1943.

Barron studied 22 sheep embryos ranging in length from 5.5 to 44 mm. and in age from 21 to 40 days. The spinal cords were prepared with silver technics. At the 22 day stage the roof and floor plates are formed, and the sulcus limitans and the mantle layer are present. A primary grouping of neuroblasts is seen as early as the twenty-first day. By the thirty-fourth day the lateral mass of neuroblasts has given rise to ventrolateral, dorsolateral, central and retrodorsal groups. Baron finds that the motor cell columns in the anterior cervical and brachial segments of the cord are all laid down at the time the embryo first becomes active. At that time the cell columns are in their final position, but their development is incomplete.

FRASER, Philadelphia.

Physiology and Biochemistry

STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT: IV. MENTAL CHANGES IN EXPERIMENTAL DEFICIENCY. HARRIET E. O'SHEA, K. O'SHEA ELSOM and RUTH V. HIGBE, Am. J. M. Sc. **203**:388 (March) 1942.

O'Shea, Elsom and Higbe undertook to measure objectively the psychologic status of the adult human subject receiving an experimental diet deficient in the B vitamins. Psychologic tests were administered to 4 voluntary subjects taking an experimental diet and to 4 normal controls who consumed an adequate diet. Each subject consumed a diet which supplied an adequate quantity of all dietary factors except the B vitamins. There were three experimental periods: (1) the period when the subjects received the experimental diet alone; (2) the period when thiamine hydrochloride was added to the diet, and (3) the period when the vitamin B complex (brewers' yeast or synthetic vitamin B complex) was administered. Each subject and each control were subjected to four psychologic test series. The special mental functions studied were speed of coordination of the hand muscles, intelligence, reasoning ability (reading), foresight and judgment, prose memory and visual and auditory memory. The subjects succeeded less well in solving the mazes when deficient in the B vitamins than after receiving thiamine hydrochloride or the vitamin B complex. There was a definite relation between the degree of deficiency and the degree of impairment of maze performance. The results indicated that an impaired maze performance is a significant manifestation of deficiency of the B vitamins. No significant differences were observed in intelligence test scores during deficiency or after therapy, indicating that adult intelligence test performance does not deteriorate during deficiency of the B vitamins nor does it improve after therapy with these substances. Reasoning ability (reading) and speed of hand muscle coordination (tapping) showed no measurable deterioration when the subjects were deficient in the B vitamins and no improvement after therapy with thiamine hydrochloride or with the vitamin B complex.

MICHAELS, Boston.

INDEPENDENT DIFFERENTIATION OF THE SENSORY AREAS OF THE AVIAN INNER EAR. HIRAM J. EVANS, Biol. Bull. **84**:252, 1943.

Differentiation of the sensory areas of the avian inner ear has been studied by transplantation of isolated primordia of the inner ear to the chorioallantoic membrane. Maculas, cristae and a papilla basilaris differentiated in the transplants. The sensory areas of the transplanted labyrinths are comparable to those of the control. The morphogenesis of the membranous labyrinth was greatly suppressed in the grafts, but the histogenesis of the sensory components showed little retardation. Since the sensory areas of the inner ear undergo typical development when isolated from their nerve supply, Evans concludes that they are capable of differentiating independently of the nervous system.

COBB, Boston.

ACID-SOLUBLE PHOSPHORUS COMPOUNDS OF CEREBRAL TISSUE. WILLIAM E. STONE, J. Biol. Chem. **149**:29, 1943.

Analysis of cerebral tissue after fixation in situ with liquid air seems to offer the nearest presently available approach to the chemical composition of the brain in the living animal. Studies of acid-soluble phosphorus compounds by this method have demonstrated the presence of inorganic phosphate, phosphocreatine, adenosine triphosphate and possibly guanosine triphosphate. There still remains a quantity of organic acid-soluble phosphorus compounds which have not been chemically identified. An improved method is presented for the fractionation of the acid-soluble phosphorus compounds of cerebral tissue. A procedure is described for the determination of the ribose component of the nucleotides. The unidentified organic acid-soluble phosphorus compounds of cerebral tissue include at least three distinct substances: (*a*) one which behaves like hexose-6-monophosphate; (*b*) one which is thought to be aminoethyl phosphate, and (*c*) an ethanol-soluble substance. Attempts to detect the presence of phosphoglycerate, triose phosphate and phosphopyruvate in cerebral tissue were unsuccessful. The principal changes observed to occur during thirty minutes of postmortem autolysis of cerebral tissue are the hydrolysis of phosphocreatine and the partial decomposition of adenosine triphosphate. The methods used indicate the presence of adenosine diphosphate, adenylic acid, a nucleoside or free pentose and inorganic phosphate among the decomposition products of adenosine triphosphate.

PAGE, Indianapolis.

PITRESSIN DIAGNOSIS OF IDIOPATHIC EPILEPSY. W. BLYTH, Brit. M. J. **1**:100 (Jan. 23) 1943.

Blyth describes a method of precipitating convulsive seizures in patients who claim to have or are suspected of having idiopathic epilepsy. It is of particular value with patients

whose attacks occur at infrequent intervals. The rationale of the method is based on the fact that retention of water in the body will precipitate the seizure in predisposed persons but will affect normal persons but little. Retention of water is obtained by the oral administration of copious amounts of water, together with intramuscular injection of pitressin. The method is contraindicated in the presence of diabetes, nephritis, arteriosclerosis or myocarditis. Blyth used the procedure with 87 patients suspected of having idiopathic epilepsy, the diagnosis for 86.6 per cent of whom was verified by the test.

ECHOLS, New Orleans.

AN ACTION OF ADRENALIN ON TRANSMISSION IN SYMPATHETIC GANGLIA, WHICH MAY PLAY A PART IN SHOCK. EDITH BÜLBRING and J. H. BURN, J. Physiol. **101**:289, 1942.

Bülbring and Burn studied the transmission of nerve impulses in sympathetic ganglia in eviscerated dogs in which the sympathetic ganglia were perfused. In small amounts epinephrine augmented the transmission of impulses in the ganglia but depressed it in large amounts.

In atropinized cats small doses of epinephrine augmented the ganglionic action of acetylcholine, but larger doses depressed it. In a spinal cat the pressor effect of splanchnic stimulation was increased by continuous perfusion of epinephrine, but single large doses depressed the response. This depression was accompanied by a fall in the general blood pressure. The authors express the opinion that the latter action may occur in certain cases of shock.

THOMAS, Philadelphia.

THE EFFECT OF VARIATIONS IN THE SUBARACHNOID PRESSURE ON THE VENOUS PRESSURE IN THE SUPERIOR LONGITUDINAL SINUS AND IN THE TORCULAR OF THE DOG. T. H. B. BEDFORD, J. Physiol. **101**:362, 1942.

Contrary to the conclusions previously reached by Becht and by Weed and Flexner, Bedford finds that any considerable increase in subarachnoid pressure is accompanied by a decrease in venous pressure in the superior longitudinal sinus and in the torcular.

A rapid increase in subarachnoid pressure from the pressure level of the cerebrospinal fluid to 500 mm. of isotonic solution of sodium chloride was invariably accompanied by a fall in venous pressure, which averaged 20 mm. of isotonic solution of sodium chloride. The fall in venous pressure was less when the subarachnoid pressure was elevated more slowly; for example, it fell on an average about 10 mm. when the subarachnoid pressure was elevated at the rate of 100 mm. per minute. The venous pressure returned to normal when the subarachnoid pressure was lowered to its original level.

THOMAS, Philadelphia.

EFFECT OF BONE DYSPLASIA ON CRANIAL NERVES IN VITAMIN A-DEFICIENT ANIMALS. E. MELLANBY, J. Physiol. **101**:408, 1943.

When young dogs are brought up on diets deficient in vitamin A and carotene, local overgrowth of certain bones of the skull causes compression, twisting and lengthening of most of the cranial nerves, some of which show extensive degenerative changes. The destructive changes are chiefly confined to the sensory nerves, the motor cranial nerves for the most part escaping. Motor nerves often suffer compression, lengthening and twisting as a result of overgrowth of bone, but show no degeneration.

In the experiments described, the nerves most affected were the cochlear and vestibular divisions of the eighth cranial nerve, especially the former; the first and second branches of the fifth cranial nerve and the second and first cranial nerves. Apparently, the reason for the greater susceptibility of the sensory nerves lies in the compression not only of the nerve fibers but of the ganglia.

Degeneration in the optic nerve may be produced in vitamin A–deficient animals not only by direct pressure of overgrown bone and by increased intracranial pressure but by a primary degenerative change, beginning in the retina itself. The early optic nerve atrophy associated with bleaching of the tapetum is probably a direct effect of the vitamin A deficiency on retinal cells.

In experiments in which the calcium intake was high the increased growth of certain bones appeared to be due to formation of an excess of cancellous tissue.

THOMAS, Philadelphia.

SYNTHESIS OF ACETYLCHOLINE IN SYMPATHETIC GANGLIA AND CHOLINERGIC NERVES. W. FELBERG, J. Physiol. **101**:432, 1943.

Sympathetic ganglia, such as the superior cervical ganglion, and cholinergic nerves, such as the cervical portion of the sympathetic trunk, the vagus and phrenic nerves and the motor

roots, if divided with scissors into small pieces and incubated for one to two hours in buffered saline solution containing physostigmine, are still able to synthesize acetylcholine. This property is lost if the nerves are ground with silica. Sensory nerve roots yielded no acetylcholine on extraction and failed to synthetize it under conditions which gave evidence of synthesis when motor nerves were used.

When the cervical part of the sympathetic trunk is cut in a preliminary operation, the distal part of the nerve and the superior cervical ganglion lose their property of synthesizing acetycholine after about forty-eight hours. This loss precedes the loss of nerve conduction. In the ganglion it coincides with the time when synaptic transmission becomes impaired and lost. Felberg concludes that synthesis of acetylcholine in sympathetic ganglia is a property of the preganglionic endings and is a necessary preliminary to normal, particularly sustained, synaptic transmission.

THOMAS, Philadelphia.

SYNAPTIC POTENTIALS AND TRANSMISSION IN SYMPATHETIC GANGLION. J. C. ECCLES, J. Physiol. **101**:465, 1943.

When synaptic transmission through a sympathetic ganglion is blocked by curare, stimulation of the preganglionic fibers sets up a local negative potential of the ganglion cells in relation to their axons. Eccles terms this the synaptic potential, and he states that it spreads decrementally along the postganglionic fibers. After an initial rapid rise, it reaches a flat-topped summit at ten to twenty milliseconds and decays slowly.

In these respects the synaptic potential resembles a catelectrotonic potential and thus is analogous to the end plate potential of curarized muscle. Summation of the synaptic potentials is set up by two preganglionic volleys. If the summated potential is high enough, the ganglion cells discharge impulses. The bearing of these results on the theories of synaptic transmission is discussed.

THOMAS, Philadelphia.

Psychiatry and Psychopathology

ONE HUNDRED CASES OF INDECENT EXPOSURE. ALEX J. ARIEFF and DAVID B. ROTMAN, J. Nerv. & Ment. Dis. **96**:523 (Nov.) 1942.

Arieff and Rotman analyze 100 unselected cases of sexual exhibitionism, the most common sex offense seen at the Psychiatric Institute of the Municipal Court of Chicago. All the offenders were males, and the peak age was in the third decade. Only 4 patients were Negroes. The offense almost invariably occurred at home or in a public place, and a majority exposed themselves in broad daylight. As a whole, the patients were of low economic and cultural status. Sixty-two persons were single and 38 married; thus marriage, obviously, does not constitute a cure for the condition. Most of the exhibitionists had been previously arrested on various charges. The authors divide the patients into two groups: (1) institutional, made up predominantly of mentally defective, schizophrenic and senile persons, and (2) noninstitutional, composed of persons with psychopathic conditions, compulsive neuroses, borderline mental deficiencies and schizoid states. Previous sexual irregularity was frequent. The authors believe that the offense is evidence of severe personality maladjustment. They regard the act as an asocial aberration of the socially acceptable exhibitionism which is a preliminary stage of mating.

CHODOFF, Langley Field, Va.

PHYSICAL, PSYCHIATRIC AND PSYCHOMETRIC STUDIES OF POST-ENCEPHALITIC PARKINSONISM. DONALD SHASKAN, HELEN YARNELL and KAREN ALPER, J. Nerv. & Ment. Dis. **96**:652 (Dec.) 1942.

Twenty-seven patients with postencephalitic parkinsonism were treated with large doses of an alkaloid of the atropine group, little difference being noted whether atropine, scopolamine or stramonium was used. Since factors other than the effect of the drug were thought to be important, psychiatric and psychologic studies were carried out. The patients studied psychiatrically gave histories of an insecure childhood. They had poorly adjusted personalities and tended to find a satisfactory adjustment in their illness. Two patients with oculogyric crises showed compulsive phenomena, in agreement with the observations of Jelliffe. A group subjected to a battery of psychologic tests showed a considerable degree of reduction in intellectual efficiency. The most notable defects were slowness of association, difficulty in performing mental shifts, inability to organize parts into a simple gestalt unit and specific failing of memory. Drawings of a man were interpreted as illustrating either sexual preoccupation or intellectual impairment. Rorschach records showed that all patients made some effort to

adjust to their disabilities. Narrowing of the range of interests, anxiety, depression and sensitivity to body disability were all prominent in the Rorschach records.

CHODOFF, Langley Field, Va.

A COMPARISON OF SCHIZOPHRENIA AND MANIC-DEPRESSIVE WITH REFERENCE TO EMOTIONAL MATURITY. M. A. DUREA, J. Nerv. & Ment. Dis. **96**:663 (Dec.) 1942.

Persons with schizophrenia surrender to difficulty by regressing, while patients with manic-depressive disorders surrender but do not regress. The degree of emotional maturity attained is a fundamental factor in both conditions. Durea attempts to appraise this factor by the use of the interest-attitude test of Pressey with a group of patients with manic-depressive psychoses, a group with schizophrenia and a control group. With this method both the pathologic groups were inferior in emotional age to the control group, but the median scores for the schizophrenic patients (except in one subtest) were lower than those for the manic-depressive patients. Schizophrenic patients were most retarded emotionally according to test II (worries) while manic-depressive patients were most retarded according to test IV (admirations). The author suggests that emotional retardation is a function of the tendency to regression.

CHODOFF, Langley Field, Va.

CRYPTIC NOSTALGIA. C. L. WITTSON, H. I. HARRIS and W. A. HUNT, War Med. **3**:57 (Jan.) 1943.

In the usual cases of nostalgia the subject shows a mild reactive depression, with mild retardation, agitation and tearfulness. He has insight into the cause of his feelings. The authors describe another type which is met with in the armed services. The soldier is apathetic, absent-minded, slow in responding, inattentive and unable to concentrate and fails to carry out routine duties. He seems preoccupied. He apparently has adjusted to his new environment adequately. He fails even to notice that there is something wrong with him and has no insight into its cause. Such a state may be confused with schizophrenia or with feeblemindedness because sometimes the patient does poorly in a psychometric examination.

Psychiatric interview reveals that the patient is preoccupied constantly with thoughts and memories of home. The condition is not homesickness but a fixation on home and family. It is possible usually to give him insight into his condition, which generally clears up entirely as a result of a single interview.

PEARSON, Philadelphia.

Diseases of the Brain

EPIDEMIOLOGIC ASPECTS OF ENCEPHALITIS IN YAKIMA VALLEY, WASH. W. M. HAMMON and B. F. HOWITT, Am. J. Hyg. **35**:163 (March) 1942.

From the inductive epidemiologic analysis of 86 cases of encephalitis in human beings and of 20 cases of encephalomyelitis in horses in 1939 and 1940, it appears to Hammon and Howitt that both the western equine virus and the St. Louis virus were present in Yakima Valley simultaneously and produced some instances of mixed infection. Neutralization tests of the blood serum of 50 patients showed 84 per cent to be positive for the western equine virus, 72 per cent for the St. Louis virus and 56 per cent for both viruses. The serum from 75 closely comparable controls from the general population disclosed neutralizing antibodies for the western equine virus in 6.7 per cent, for the St. Louis virus in 28 per cent and for both in 2.7 per cent. The figures for patients and controls were compared with those obtained for serum from other areas in the West, and the difference helped to establish the presence of the St. Louis virus in the serum of Yakima patients as etiologically significant. The serum of a few normal chickens, pheasants and a duck were found to neutralize the western equine virus, and the blood of some horses neutralized the St. Louis virus. Suggestive correlation was found between the occurrence of antibodies in patients only to the St. Louis virus and contact with, or proximity to, horses, an observation which may be significant, since antibody to this virus was found in horses.

J. A. M. A.

CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS IN SEVERE EPILEPSY UNDER TREATMENT. DOUGLAS GOLDMAN, Am. J. M. Sc. **205**:388 (March) 1943.

Goldman reports the result of a study of 16 patients with severe epilepsy for from two months to three years with the aid of electroencephalograms during determination of the effects of medication, chiefly with diphenylhydantoin sodium and phenobarbital. Most of the patients were inmates of a state hospital for mental illness whose psychoses were manifestations of the convulsive disorder. In every instance the protocols which accompanied the electro-

encephalogram revealed that the tracing was correlated with the clinical evidence. The author concludes that adequate, vigorous and, above all, sustained treatment of convulsive disorders in their early stages, preferably under electroencephalographic control, may restore patients to complete freedom from seizures and protect them from late sequelae, such as psychoses.

MICHAELS, Martinsburg, W. Va.

CHOREA COMPLICATING POLYCYTHEMIA VERA. LAURENCE M. KOTNER and JOHN H. TRITT, Ann. Int. Med. **17**:544 (Sept.) 1942.

Kotner and Tritt report the case of a white woman aged 64 with chorea and polycythaemia vera, the fifth case of the kind to be reported and the first instance in the literature in which autopsy was performed on a person with such a condition. Thrombi were observed only in the smaller veins of the brain, with no predilection for localization in the basal ganglia or in the area immediately adjacent to them. Both cerebral hemispheres showed widespread involvement. The xanthochromic and bloody appearance of spinal fluid obtained shortly before death was explained by a small hemorrhagic area in the choroid plexus of the fourth ventricle.

PRICE, Philadelphia.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. CLEMSON MARSH, Bull. Los Angeles Neurol. Soc. **7**:182 (Dec.) 1942.

Marsh reports a study of 145 cases of neurosyphilis in which the disease was verified at autopsy; a disagreement between the clinical and the pathologic diagnosis was often noted. The most common errors in diagnosis were due to (1) incomplete study of the patient because of sudden death; (2) failure to recognize the minimal signs of chronic meningeal syphilis; (3) inaccurate classification of well defined cases of neurosyphilis, and (4) tendency to make a general diagnosis of neurosyphilis without differentiation of the form.

The author states that the various types of neurosyphilis are still proved pathologically to be fairly clearcut entities and that in most cases the patient should present fairly definite clinical symptoms. A diagnosis of a combined type of neurosyphilis, such as dementia paralytica, tabetic form, generally is wrong, the symptoms being due usually to multiple vascular lesions or to a syphilitic entity plus some other disease.

LESKO, Bridgeport, Conn.

LOSS OF EMOTIONAL EXPRESSION AND BODY SCHEME. ARNOLD P. FRIEDMAN and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **7**:206 (Dec.) 1942.

Friedman and Nielsen report 3 cases in which there were illusion of absence of a minor limb and loss of ipsilateral emotional expression. They believe that this syndrome may be due to a deep lesion close to the thalamus.

LESKO, Bridgeport, Conn.

DISORIENTATION AND ASSOCIATED GERSTMANN SYNDROME FROM INTRACEREBRAL HEMORRHAGE. ARTHUR M. PETTLER and AIDAN A. RANEY, Bull. Los Angeles Neurol. Soc. **7**:207 (Dec.) 1942.

Pettler and Raney report a case of a waitress aged 39 in whom a convulsion suddenly developed on the right side and a subarachnoid hemorrhage was noted. A short time later right homonymous hemianopsia, amnesic aphasia, alexia, agraphia, acalculia, disorientation and "finger agnosia" developed, and operation revealed a subcortical hematoma in the lower parietal and the posterior temporal region on the left side. After operation she continued to show the same mental defects as before.

LESKO, Bridgeport, Conn.

ACUTE CARDIO-VASCULAR COLLAPSE AFTER INSULIN SHOCK TREATMENT. ANDRÉ A. WEIL, J. Nerv. & Ment. Dis. **96**:556 (Nov.) 1942.

Weil reports a case in which, shortly after the termination of insulin coma, there occurred an acute cardiovascular collapse, with cessation of heart action. Two ampules of epinephrine hydrochloride (1:1,000) injected into the heart at fifteen second intervals produced resumption of the heart beat and recovery. Cardiac changes during hypoglycemia are due both to increased venous return to the right side of the heart and to a central release of parasympathetic function secondary to cerebral anoxemia. Despite this, few cardiovascular accidents have been reported during shock treatment, although cardiac and pulmonary failures have both been mentioned. The occurrence of the symptoms in Weil's case after the coma had been terminated by carbohydrates is attributed to a reactive rise in the insulin and epinephrine levels, with their subsequent effects. In spite of this, the case illustrates that at least in some instances intracardiac administration of epinephrine is a life-saving measure.

CHODOFF, Langley Field, Va.

A New Pyramidal Sign of Great Frequency. Lane Allen and Hervey Cleckley, J. Nerv. & Ment. Dis. **97**:146 (Feb.) 1943.

In an attempt to elicit from the toes a reflex comparable to the Hoffmann sign of the hand, Lane and Cleckley have discovered a new sign of disease of the pyramidal tract which they believe to occur frequently. With the leg relaxed and the foot in slight plantar flexion, the second toe is flicked sharply upward with the finger applied to the ball of the toe. A positive result is indicated by a quick and transient dorsiflexion of the great toe and sometimes of the lesser toes. The maneuver is similar to that described by Rossolimo and sometimes elicits the Rossolimo reflex. The new sign, referred to as hallux extension, is extremely sensitive and may appear with slighter impairment of function of the pyramidal tract than is necessary to produce the Babinski or the Rossolimo sign. The authors suggest that the new sign may result from damage to area 6, and that it is an early and very sensitive, although not absolute, indication of pyramidal dysfunction.

Chodoff, Langley Field, Va.

A Case of Cerebellar Atrophy. Mogens Ellermann, J. Nerv. & Ment. Dis. **97**:389 (April) 1943.

Ellermann reports the case of a man aged 65 who, at the age of 4½ years, sustained a severe injury to the head, followed by behavior difficulties and failure of mental development. Between the ages of 35 and 40 signs of cerebellar disease gradually appeared, with ataxic gait, intention tremor and dysarthria. At about the age of 44 he was hospitalized with an atypical and grandiose type of psychosis, later marked by psychic dissolution. Pneumoencephalographic examination revealed pronounced cerebellar atrophy. In view of the late development of the cerebellar syndrome, a traumatic origin was considered unlikely. Because of the purity of the cerebellar picture, the case is classed as one of abiotrophy, probably a primary parenchymatous atrophy of the cortex of the type first described by Marie, Foix and Alajouanine.

Chodoff, Langley Field, Va.

Cerebellar Extradural Hematoma. F. K. Kessel, J. Neurol. & Psychiat. **5**:96 (July-Oct.) 1942.

Kessel reports the case of a woman aged 24 who sustained an injury to the back of her head, followed by unconsciousness and vomiting. After a lucid interval of thirty hours, in which only severe headache was experienced, cerebellar fits suddenly set in, followed by deepening unconsciousness. Roentgenograms showed only slight separation of the left half of the lambdoid suture. A cerebrospinal fluid block was demonstrated. An extradural hematoma was encountered over the left cerebellar hemisphere, the hemorrhage originating from rupture of the left transverse sinus. The hematoma was evacuated and the cisterna opened wide to relieve the increased intracranial pressure. Complete recovery followed. The author believes that the cerebellar fits represented a special form of decerebrate rigidity and may have resulted from disturbed intracranial circulation. Isolated extradural cerebellar hematoma is extremely rare and, according to the author, is always due to laceration of the transverse sinus or one of its tributary veins. It is usually accompanied by fracture of the skull. The low pressure within the transverse sinus may account for the slow development of the hematoma. The lesion frequently presents a diagnostic problem, which is rendered less difficult when cerebellar fits are present. Unless the condition is recognized early, the prognosis is usually bad.

Malamud, Ann Arbor, Mich.

Fatal Intracranial Venous Haematoma Following Ventricular Drainage. J. Schorstein, J. Neurol. & Psychiat. **5**:142 (July-Oct.) 1942.

Schorstein reports 3 cases in which death resulted from intracranial hemorrhage following ventricular drainage. In all 3 cases chronic internal hydrocephalus with increased intracranial pressure was present, caused in 2 instances by obstruction of the aqueduct near its commencement and in the third case by adhesive arachnoiditis blocking the foramen of Magendie. In the first 2 instances the hemorrhage was extradural, while in the third it was subdural and intracerebral. The bleeding was probably of venous origin, derived from the rupture of dural veins. In all 3 cases the extracerebral clots overlay the frontal lobes. The author attributes the hemorrhages to the reduction of intracranial pressure by the ventricular drainage. This decreased pressure causes the dura to become detached from the bone and, aided by traction on the dura by way of the venous anchorage of the brain, results in rupture of veins passing between the dura and the skull. The venous pressure, which exceeds the cerebrospinal fluid pressure when drainage is instituted, aids still further the expansion of the clot from the ruptured veins. Young persons with chronic hydrocephalus are the ones most likely to have a complication.

Malmud, Ann Arbor, Mich.

ABSCESS WITHIN THE SELLA TURCICA SIMULATING PITUITARY TUMOR: SURGICAL CURE. H. J. SVIEN and J. G. LOVE, Proc. Staff Meet., Mayo Clin. **17**:497 (Sept. 23) 1942.

Isolated reports of metastatic abscess in the sella turcica are known, but primary abscess of the pituitary is rare. So far as Svien and Love are aware, no cases of the latter have been recorded. Their patient, a woman aged 34, complained of headache and vomiting. At the age of 21, five months after the birth of a child, her menses ceased, and immediately after the birth of her child diabetes insipidus developed, which was relieved temporarily by solution of posterior pituitary U. S. P. This condition became less severe during the four years preceding entrance into the hospital. There developed severe pain in the left side of the head, which extended from the left eye into the neck and was associated with blurred vision, nausea and vomiting. For several months she had noticed loss of vision in the left field. Examination revealed normal fundi and bitemporal hemianopsia. The sella turcica was observed to be enlarged. A diagnosis of a chiasmal lesion was made; a transfrontal craniotomy was performed, and an abscess, occupying the sella turcica, was encountered. About 15 cc. of pus was aspirated, and sulfanilamide crystals were placed within the abscess cavity and sprinkled around the optic nerves and the chiasm. No growth was obtained from the pus. Convalescence was uneventful save for the development of left hemiplegia and hemianesthesia on the seventh postoperative day. This disappeared spontaneously in several days. The fundi remained normal, and the visual fields returned to normal. No focus for the abscess was determined.

ALPERS, Philadelphia.

PARAPHYSIAL CYSTS OF THE THIRD VENTRICLE. LAURENCE M. WEINBERGER and BENJAMIN BOSHES, Surgery **13**:368, 1943.

Weinberger and Boshes report a case of paraphysial cyst of the third ventricle successfully removed at operation, it being the seventeenth instance thus far recorded in which surgical recovery resulted. The patient was a woman aged 22 with a history of headache and vomiting for three weeks. Some weeks after operation the patient recalled that the headaches were associated with changes in posture, being either caused or intensified by her assuming a recumbent position. Neurologic examination on her admission to the hospital revealed merely a high degree of papilledema and palsy of both external rectus muscles. Localization was determined by ventriculographic means, both lateral ventricles were greatly dilated, and air was not visualized in the third ventricle. Both intraventricular foramens were sharply cut off. Operation was performed through a right frontal osteoplastic bone flap and a transcortical incision into the right lateral ventricle. The tumor was removed by drawing it through the foramen of Monro into the lateral ventricle, where its attachment to the choroid plexus was coagulated and cut. The patient made a good postoperative recovery, marred only by transient left hemiparesis and a jacksonian seizure on the left side five days after operation. Four months later she was entirely well, and the neurologic status was normal.

The authors point out that there is no syndrome typical of tumors of this kind, but it is often recorded that headache is noticeably affected by changes in position of the head, the so-called ball valve phenomenon. Diagnosis is dependent on the evidence afforded by pneumography.

SHENKIN, Philadelphia.

OSTEOCHONDROMAS ARISING FROM THE BASE OF THE SKULL. CARL FELIX LIST, Surg., Gynec. & Obst. **76**:480, 1943.

List reports 7 cases of osteochondroma of the skull, the tumor in 5 being primarily intracranial, arising from the sphenoid bone, and in 2 primarily extracranial, arising from the ethmoid or sphenoid region, with secondary intracranial extension. All the primary osteochondromas originated from the sphenoid bone and extended intracranially into the posterior parasellar region. One of them was but the intracranial manifestation of generalized chondromatosis. The characteristic site of the tumors makes it probable that they develop from residuals of the cartilaginous primordial cranium. The author notes that chordomas are found in a location similar to that of osteochondromas, viz., at the junction of the basisphenoid and the basiocciput.

Osteochondroma is usually seen in young adults and grows slowly; hence a course of over ten to twenty years is not unusual. Intracranial osteochondroma produces a neurologic syndrome characteristic of its parasellar location. A primarily extracranial osteochondroma produces symptoms at first characteristic of an expansive or obstructive lesion of the paranasal sinuses. Later, as the tumor penetrates the cranial cavity, the optic nerve is first involved, and later a parasellar syndrome may be produced. Roentgenograms are almost pathognomonic.

The treatment is surgical. The prognosis is good, providing malignant change in the tumor has not occurred. Recurrence ultimately results, however, since only partial removal is possible at operation.

SHENKIN, Philadelphia.

EFFECT OF PNEUMOENCEPHALOGRAPHIC TESTS ON EPILEPSY AS PROVED BY ELECTROENCEPHALOGRAMS. RICARDO MOREA and JOSE B. ODORIZ, Rev. neurol. de Buenos Aires **7**:207 (July-Sept.) 1942.

Morea and Odoriz report 3 cases of epilepsy in which electroencephalographic studies were made before and after injection of air into the lumbar subarachnoid space. In all 3 cases the electroencephalographic patterns were typical of grand mal. In 2 of the cases clinical improvement followed pneumoencephalographic study, the electroencephalographic tracings in both cases reverting to normal or near normal. In the third case there was no improvement, either clinical or electroencephalographic. The authors conclude that pneumoencephalography is of definite value as a therapeutic measure in the management of epilepsy.

PIETRI, New York.

ENCEPHALITIS FOLLOWING INCLUSION CONJUNCTIVITIS. F. BAMATTER, Confinia neurol. **4**:314, 1942.

Bamatter reports 3 cases of encephalitis occurring in association with inclusion conjunctivitis in newly born infants. There were associated inflammatory hydrocephalus and albuminocytologic dissociation in the cerebrospinal fluid. The author states that while it has not been proved that keratoconjunctivitis with inclusion bodies and encephalitis in such infants have a common etiologic factor, the associated clinical manifestations are striking. He believes that this variety of encephalitis constitutes a clinical entity which has not been hitherto described.

DEJONG, Ann Arbor, Mich.

Peripheral and Cranial Nerves

THE PROBLEM OF PRIMARY SCIATIC NEURITIS: AN ANALYSIS OF 55 CASES. B. J. ALPERS, H. S. GASKILL and B. P. WEISS, Am. J. M. Sc. **205**:625 (May) 1943.

Alpers, Gaskill and Weiss, impressed with the inconsistencies in the literature, reviewed their cases of sciatic neuritis in order to establish the incidence of sciatic neuritis and to determine its differentiation from other types of sciatica. Of 55 patients, 37 (67 per cent) were males and 18 females. All but 4 of the males were engaged in heavy work; most of the females were housewives. The age incidence varied from 16 to 72 years, the majority of the patients (41, or 73 per cent) being between the ages of 30 and 60. Pain referable to the hip or leg of one side was the presenting symptom of the majority of patients. Pain in the back was present only in 17 (30 per cent) of the patients; it is more common with secondary sciatica. In 3 patients pain in the leg was bilateral; in all the others it was unilateral. The location of the pain in the leg varied widely. In 29 patients the pain extended from the thigh, in the region of the hip, to the ankle, toes or heel. The pain in 29 patients lasted from one to twelve weeks, in 9 patients from three to six months and in 13 patients from one to five years. The patients, 13 (23 per cent), in whom it persisted for one year or more had recurrent attacks of sciatic neuritis. Mere prolongation of symptoms does not indicate a secondary cause of the sciatica unless other evidence, such as roentgenographic changes in the vertebrae and increased protein in the spinal fluid, is present.

Only 7 of the 55 patients had paresthesias. None had incontinence of the bladder or rectum. Tenderness of the nerve was found in 46 of 55 patients, and it was usually noted everywhere along the sciatic trunk. Lasègue's sign was absent in only 7 patients. The achilles reflex was decreased or absent on the side of the neuritis in 36 patients. Muscular weakness was not encountered. Sensory changes occurred in only a few patients, with a slight decrease in pain sensation over the lateral aspect of the thigh or leg. Foci of infection constituted one of the outstanding causes and included diseased tonsils (28 patients), carious teeth (20 patients), sinusitis (12 patients) and prostatitis (8 patients). Osteoarthritis of the sacroiliac joint or of the lumbar vertebrae was observed in 17 patients. Of diagnostic importance is tenderness of the nerve trunk, particularly in the sciatic notch and the popliteal space; this symptom was present to some degree in every patient. Severe tenderness of the nerve trunk was noted in 22 patients, moderate tenderness in 24 patients and mild tenderness in 9 patients. The authors believe that true sciatic neuritis is not rare.

MICHAELS, Martinsburg, W. Va.

ALBUMINOCYTOLOGIC DISSOCIATION IN THE SPINAL FLUID WITH XANTHOCHROMIA. KARL O. VON HAGEN, Bull. Los Angeles Neurol. Soc. **7**:198 (Dec.) 1942.

Von Hagen reports 2 cases of infectious neuronitis (Guillain-Barré syndrome) with xanthochromia. The cases are of interest because xanthochromia has been reported to be of unusual occurrence in cases of infectious neuronitis. LESKO, Bridgeport, Conn.

FACTORS AFFECTING RECOVERY OF MOTOR FUNCTION AFTER NERVE LESIONS. E. GUTMANN, J. Neurol. & Psychiat. **5**:81 (July-Oct.) 1942.

Recovery of the motor function of a muscle begins with its reinnervation but is complete only after a series of steps in the process of "functional completion" have taken place. To test this, Gutmann crushed the peroneal nerve at the knee in rabbits and observed the gradual recovery of ability to spread the toes. He found that new axons returned to the muscle in ten days, contraction of the muscle on stimulation of the nerve in eighteen to twenty days, the first reflex function in twenty-five days and full reflex function eight days later. The circumference of the denervated muscle began to increase and its threshold to direct stimulation to decrease before reflex function, and sometimes even before direct excitability, returned. After reappearance of reflex function fibrillation continued in the muscles for about two weeks; the normal weight of the muscle was regained about twelve weeks afterward.

The following factors influence the recovery of function: 1. The level of the lesion. The time between the beginning of functional recovery of the muscle and its completion is greater the more distant the lesion from the muscle, but the rate of nerve regeneration remains fairly constant and does not depend on the level of the lesion. 2. The type of injury. Recovery is slower after severance and suture than after crushing of a nerve, even if the latter is carried out over a distance of 4 cm. This may be due to slower advance of the process of regeneration and the shunting of fibers into wrong channels with the former method. When the nerve is crushed a second time, sixteen to forty-two days after the initial injury, recovery occurs earlier than after a single crush, a fact which may be attributed to a surplus of Schwann cells produced by the second interruption. 3. Interference with the blood supply to the limb. This does not delay the recovery of the muscle. 4. Cross union, such as that between the central stump of the tibial nerve and the peripheral stump of the peroneal nerve, leads to limited recovery of function. This does not imply central relearning, since the tibial nerve contains some fibers which innervate muscles normally producing spread of the toes. 5. Delayed suture. This tends to retard recovery, but the effect is pronounced only when the delay exceeds six months. 6. Infection. The effects vary from delayed recovery to no appreciable influence. 7. Age. Recovery tends to be more speedy in young animals than in old ones.

MALAMUD, Ann Arbor, Mich.

PROCAINE NERVE BLOCK IN THE INVESTIGATION OF PERIPHERAL NERVE INJURIES. W. BREMNER HIGHET, J. Neurol. & Psychiat. **5**: 101 (July-Oct.) 1942.

According to Highet, peripheral nerve block affords a useful method of investigating the function of peripheral nerves. The technic employed by the author consists of injection of a 2 per cent solution of procaine containing epinephrine in a concentration of 1:50,000 and the use of an apparatus designed for direct unipolar stimulation of the nerve into which the solution is injected. The criteria of completeness of the nerve block thus produced are: (*a*) full vasodilatation, anhidrosis, anesthesia and analgesia in the autonomous zone of the nerve and (*b*) complete and lasting paralysis of muscles supplied by the nerve distal to the site of the block. The method has been useful in investigation of the following problems: 1. Anomalous innervation of muscles. 2. "Supplementary" and "trick" movements. The former are performed at a joint by the contraction of muscles which are able to take over the function of the paralyzed muscles. These movements are to be distinguished from true trick movements, which are passive and are brought about by tension on paralyzed muscles due to the overaction of their antagonists, by "rebound" or by the action of gravity. 3. Sensory and sudomotor distribution of peripheral nerves. One must take into account factors due to nerve overlap, such as the difference in extent between the autonomous and the maximal zone of sensory distribution and the initial progressive shrinkage of the area of sensory loss following nerve section before actual regeneration has set in. In this way one can distinguish complete from partial and recovering lesions of peripheral nerves. 4. The vasomotor distribution of peripheral nerves. The author is of the opinion that this is identical with the distribution of unmyelinated fibers subserving sweat and pain functions. In some cases of causalgia sympathetic nerve block is useful before sympathectomy is performed. MALAMUD, Ann Arbor, Mich.

FACTORS AFFECTING RECOVERY OF SENSORY FUNCTION AFTER NERVE LESIONS. E. GUTMANN and L. GUTTMANN, J. Neurol. & Psychiat. **5**:117 (July-Oct.) 1942.

In order to study recovery of analgesic areas after lesions of nerves, Gutmann and Guttmann first mapped out the maximal and autonomous zones of the cutaneous distribution of the peroneal, tibial, sural and posterolateral cutaneous nerves of the thigh and the saphenous major in the rabbit. They found that recovery of sensation after denervation may be divided into three phases: 1. Recovery in zones of overlap by the progressive resumption of function by fibers of adjacent nerves. These zones are formed where several nerves meet, the pattern depending on the anatomic supply of the subject's peripheral nerves. Pure cutaneous nerves, such as the sural, internal saphenous and lateral cutaneous, show extensive overlap on both the proximal and the distal border, whereas with mixed nerves, such as the tibial and peroneal, the overlap on the distal distribution is negligible. Recovery in zones of overlap generally occurs two to four weeks after interruption of the nerve, but in young animals it may take place after a few days. Recovery is susceptible to various factors, such as local damage of the skin supplied by adjacent nerves, transient block of these nerves as a result of operation and all processes which tend to raise nerve thresholds, such as infection, narcosis and age. 2. Recovery by local extension of fibers into the autonomous zone. This plays a role when a small analgesic area is surrounded by other nerves, but not in recovery of sensation in larger areas or with mixed nerves. 3. Recovery in the autonomous zone of a nerve by true regeneration. This proceeds in a downward direction, the recovery advancing faster at the edges than in the center, so that the analgesic area shrinks concentrically. The process is the same after a lesion of any nerve. The margin of algesia makes a general advance, so that estimation of the rate of recovery is permitted. This rate is affected by various factors, chiefly the nature of the lesion. Thus, after suture the recovery is slower than after crushing of the nerve, the rate for the latter being 3.35 mm. per day and the latent period of twenty-two days, as compared with 2.46 mm. per day and a latent period of forty days with suturing. The peripheral delay apparently depends on the arrival of new fibers and their maturation. The rate of advance of algesia is faster when the nerve is crushed at the ankle than in the thigh. Crushing the nerve over a stretch of 4 cm. delays recovery by two weeks. The greater success following crushing is apparently due to the fact that the Schwann sheaths maintain their continuity.

MALAMUD, Ann Arbor, Mich.

PARALYSIS OF LEFT RECURRENT LARYNGEAL NERVE FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTITETANIC SERUM. H. S. FLOYD, W. E. PEMBLETON and P. P. VINSON, West Virginia M. J. **38**:253 (July) 1942.

Floyd and his co-workers report what they believe to be the seventh case of paralysis of the left recurrent laryngeal nerve and of both brachial plexuses following subcutaneous prophylactic administration of 1,500 U. S. P. units of tetanus antitoxin. The patient gradually improved, and within three and a half months the function of the arms was normal. The voice gradually returned to normal, and within six months of onset the larynx appeared normal on inspection.

J. A. M. A.

INNERVATION AND FUNCTION OF THE THENAR MUSCLES. W. BREMNER HIGHET, Lancet **1**:227 (Feb. 20) 1943.

Highet cites several cases of complete division of the median nerve in which a faulty diagnosis of an incomplete or a recovering lesion was made because of good action in one or the other of the thenar muscles, which classically are innervated by the median nerve. The muscle giving rise to the greatest difficulty is the flexor pollicis brevis. Stopford stated that "the flexor pollicis brevis is composed of several slips, some supplied by the median, others by the ulnar, which are subject to considerable variation."

In a case of injury to the median nerve in which some activity is preserved in one or the other of the thenar muscles, there must be some means of deciding whether the innervation of the thenar muscles is anomalous or whether the injury to the nerve is incomplete. There are two methods of investigation: First, bipolar percutaneous faradic stimulation of the ulnar nerve just above the pisiform bone may produce a response in all intrinsic muscles of ulnar innervation. Second, a peripheral nerve block may be made. Procaine with epinephrine is injected percutaneously in or around the nerve to be tested. If the technic is satisfactory, all conduction in the nerve tested may be abolished for two to four hours. The nerve block may be performed in one of two ways: Either the injured median nerve may be blocked immediately above or below the site of injury, or, better, the nerve believed to be responsible

for the anomalous innervation of the thenar muscles is blocked. In all the cases cited by Highet this has been the ulnar nerve. A favored site of ulnar nerve block is at the level of the medial epicondyle.

Twenty cases of complete division of the median nerve are cited, with a detailed examination of the thenar muscles, both before and immediately after suture of the nerve. In this series the flexor pollicis brevis was shown to be innervated by the ulnar nerve in 16 cases (80 per cent). In 4 cases there was some action of the opponens pollicis, in addition to the flexor pollicis brevis. In 2 cases there was also some action of the abductor pollicis brevis after injury to the median nerve.

Of 25 cases of proved division of the ulnar nerve, obvious wasting of the flexor pollicis brevis was evident in only 1 case. The absence of obvious wasting and paralysis is not surprising, since the flexor brevis usually receives its innervation from both the median and the ulnar nerve. In cases of division of the median nerve the activity of the muscle is due to the preservation of its ulnar innervation and is readily noted because of the paralysis and wasting of the abductor pollicis brevis and the opponens pollicis. In cases of division of the ulnar nerve the muscle is still active because of its median innervation, wasting being obscured by the overlying abductor pollicis brevis.

SANDERS, Philadelphia.

NEURITIDES ACCOMPANYING SYPHILITIC AORTITIS. A. BERNER, Confinia neurol. **5**:13, 1942.

Berner expresses the belief that in most instances the nerves supplying and contiguous to the aorta are affected by the disease process in syphilitic aortitis. The changes observed were those of neuritis and perineuritis. Of the 15 cases studied the recurrent nerve was involved in the neighboring inflammation of the aorta in 8 and the vagus nerve in 3. Inflammatory changes in the sympathetic ganglia were often noted. The author attempts to differentiate between the nervous phenomena resulting from compression associated with dilatation of the aorta and those definitely associated with inflammatory changes in the nerves themselves.

DEJONG, Ann Arbor, Mich.

POLYNEURITIS FOLLOWING THERAPY WITH A SULFONAMIDE COMPOUND. ADHERBAL TOLOSA and CARLOS V. SAVOY, São Paulo med. **12**:269, 1939.

Tolosa and Savoy discuss the sulfonamide compounds, their uses and contraindications, and relate a case of acute gonorrhea treated with alchysulfamide (uliron). A total of 40 Gm. was given a youth aged 18 in thirteen days. About a week after cessation of the treatment the patient began to lose strength in his legs and to walk unsteadily and soon was bedridden. He had the signs of polyneuritis with tenderness of the calves, muscular weakness and absence of the achilles reflex. He was given injections of strychnine and vitamin B_1, massage and galvanotherapy. After five months he began to improve slowly. The authors note other cases of polyneuritis provoked by this drug which have been reported in the medical literature.

BAILEY, Chicago.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

WILLIAM G. LENNOX, M.D., *Presiding*

Regular Meeting, April 15, 1943

Psychiatry in an Army General Hospital. LIEUTENANT COLONEL DUNCAN WHITEHEAD, Medical Corps, Army of the United States.

A Psychodynamic Study of a Group of Patients Suffering from Arterial Hypertension. DR. CARL BINGER.

This paper is an abstract of a study made by Dr. N. W. Ackerman and myself, in collaboration with Dr. A. E. Cohn, Dr. H. A. Schroeder and Dr. J. M. Steele, of the staff of the Hospital of the Rockefeller Institute for Medical Research. The work was aided by a grant from the Josiah Macy Jr. Foundation. It will appear as a monograph, to be published by *Psychosomatic Medicine*. The personality studies were conducted by Dr. Ackerman and myself; the clinical studies, by our associates.

An effort was made to understand the life histories of 24 patients suffering from arterial hypertension in terms of motivation: to trace, in each instance, the character development, the time of onset of neurotic traits and the appearance of prodromal symptoms and of hypertension and to discover the interrelations of these events. In this paper only 1 such history is given in any detail—that of a young woman whose early childhood was threatened by great insecurity, due chiefly to her father's violent nature. The effect of this early environmental situation was worked out in relation to her whole subsequent emotional growth, and the meaning of violence to this patient was explored, with particular reference to an event of traumatic significance which was associated with the onset of her hypertension.

The existence of such traumatic situations and the emotional responses to them were described for this patient and for the others. In 23 of the 24 patients hypertension was discovered shortly after such an emotional disturbance. The failure of the integrative functions of the personality, the inefficiency of the repressive mechanisms and the inability to form organized neuroses, rather than the nature of the underlying drives, are what appear to differentiate this personality disorder from other seemingly similar ones.

Evidences of this peculiar personality are discernible before hypertension or its prodromal symptoms supervene. It may be concluded, therefore, that the "neurotic" manifestations are not the result of high blood pressure itself.

DISCUSSION

DR. STANLEY COBB: First, we of this society welcome Dr. Binger home; he spent about ten of his formative years here, and we are proud of him.

As to the work itself, he has presented many interesting observations, which were well and meticulously made. A great deal of work is needed in examining these patients and in learning about them so intimately. It is hard to make an exposition of the results in half an hour, and Dr. Binger is to be commended on presenting one excellent case and then mentioning the others. All, I suppose, would accept the mechanism of autonomic mediation of the emotions and expression of the emotions. The idea behind it all originated with Dr. Walter Cannon, who showed the effect of the emotions; we have learned about and observed such expressions in human beings. Many clinical syndromes are seen; when one of them is described as being related to a certain personality type, I become skeptical.

Among the main symptoms Dr. Binger mentions are loss of love of parents, anxiety and suppression of hate, submissiveness, suppression of warmth, stubbornness, recklessness, amnesia, lack of emotional ability to express oneself and avoidance of sex. From my own experience, I should say that these symptoms are remarkably like those I have observed in persons with Raynaud's disease. About half of them appear in persons who have arthritis; the others are rare with arthritis. They are quite unlike the personality traits seen with eczema. Persons who react with symptoms referable to the heart and circulation present about half these symptoms. That is a rough summary of experience. Does it mean that we physicians should work harder along psychologic lines, or are we barking up the wrong tree? I think we should

look up the family tree. No study of inheritance and individual susceptibility to system neurosis has been made. I believe there is a great deal in the old Adlerian idea that one inherits a weakness of one or more systems and that as one is burdened with stress that system is affected.

I was especially interested in Dr. Binger's demonstration that hypertension presents a special situation in that the symptoms are not episodic, since in all patients I have worked with they were episodic. Such patients are easier to work with because one can associate an episode with an emotional situation. I should like to ask why anxiety in one person causes renal ischemia, while in another it may produce hyperemia of the stomach, as observed by Wolff, and in another rectal hyperemia. Some women stop menstruating, and others have excessive menstruation, after a period of anxiety.

DR. REGINALD H. SOUTHWICK: (Slides were shown illustrating the pathologic physiology of the hypertensive state and the effect of surgical intervention on the vasoconstrictor pathways to the visceral vascular bed.)

DR. ROBERT S. PALMER: I appreciate hearing Dr. Binger's paper. I have been interested in the medical care of hypertensive patients and have been associated with Dr. Smithwick's work. I cannot pretend that my psychologic reviews would pass muster here. However, my associates and I have made the best psychiatric study possible of our patients. The outstanding finding is that the patient is insecure and seems to have an unusual need for success. Actually, in my experience the patients frequently have been very successful and well integrated. There is no doubt that nervous factors cause episodic increases in the blood pressure and that the level of the blood pressure and the general well-being vary directly with the general life situation. Nevertheless, hypertension, once fully established, rarely regresses to normal with psychotherapy. There are exceptions. Transient nervous hypertension in young adults, better called potential hypertension, apparently does regress, either spontaneously or with lessening of the anxiety.

It is hard to get control material except from patients without vascular disease, but I have the impression that most patients with hypertension are well organized. Perhaps the strain of integration contributes to the progress of their disease. When hypertension is discovered, there is normal concern on the part of the patient. It is hard to say at what point normal concern becomes abnormal anxiety. Certainly, when anxiety is minimal or, as in some instances, absent, the so-called hypertensive symptoms are absent. Nevertheless, when the symptom anxiety (with its physical concomitants) is relieved, the level of the blood pressure as a rule remains abnormally elevated.

In short, anxiety about the blood pressure, not the level of the blood pressure, is the precipitating cause of the symptoms in the majority of patients with mild and moderate degrees of hypertension. In my opinion, anxiety concerning the blood pressure may be a factor in the progress of the condition. This, of course, is not true in the late stage of the disease or in malignant hypertension, when either thrombosis or vascular spasm results in actual circulatory insufficiency in the brain.

DR. IVES HENDRICK: I especially enjoyed the paper from the point of view which Dr. Cobb suggested, namely, that it is a contribution not only to the study of hypertension but to the more general problems of psychosomatic disease. It is important to recognize as clearly as Dr. Binger does that one is really studying the physiologic process by two distinct methods—the laboratory and the psychologic. It is not a question of whether Goldblatt's studies of ischemia of the kidneys are relevant or of whether the psychoanalytic approach to the treatment of hypertension is relevant. Rather, there are two separate and supplementary methods of studying essentially the same problem. The psychologic approach gives a picture of what has happened emotionally, and therefore of what is happening to the autonomic nervous system as a whole; the study of the autonomic nervous system by the laboratory method is a more direct and precise approach to investigation of the organs but reveals less of the interrelations of the total organism. The author's illustrative case has shown that emotionally traumatic experience plays an important role in precipitating hypertension. It illustrates certain experiences to which a person cannot respond adequately and are therefore traumatic because they lead to a breakdown at the weak point in his physiologic equipment. What differentiates the point of breakdown in a person in whom hypertension develops from that in one in whom, say, a gastric ulcer forms, is a larger problem. How much the family history will show is a question that cannot be answered tonight. But it is reasonable to assume that a person cannot break down in a certain system unless he has some potentiality to do so. This does not mean, however, that the predisposition is entirely hereditary, that weakness of a particular system may not be due to certain experiences of infancy that are hard to investigate.

I should like briefly to compare the persons with psychosomatic disease with those who have a psychoneurosis. Dr. Binger's comment that hypertensive persons do not seem capable of organizing psychoneurotic symptoms is extremely relevant from the psychoanalytic standpoint. As Dr. Smithwick pointed out, the particular personality traits of this group do not seem to be unique in, or peculiar to, hypertensive persons. Amnesia for childhood experiences and inability to express oneself adequately, especially the inability to express one's aggression, and the fear of even feeling aggressive lead to an outward dependency and the appearance of good adjustment so long as the person can avoid situations which are acutely disturbing. This excellent relation to the environment, together with a low threshold of emotional tolerance, seems to be characteristic of hypertensive persons and of those with many of the other types of psychosomatic disease which Dr. Cobb has mentioned, such as gastric neuroses.

I should, also, like to mention that the constitutional factor of a tendency to react with instability of the neurocirculatory system is not limited to those who manifest psychosomatic symptoms. One sees it in patients with anxiety hysteria who blush easily or exhibit more frank anxiety symptoms. Patients with psychosomatic disorders do not commonly have such disease early in life, but they do have some organization of a psychologic symptom which relieves the tendency—for example, a phobia. In my opinion, it is frequently true that people who seem unusually well organized are those who are insufficiently adaptable to strain to discharge their tensions in a psychoneurotic way. From this standpoint, psychoneurosis may well be considered a blessing, a sort of safety valve which enables the person to suffer without breakdown of an organ system.

One patient had a severe psychoneurosis and died suddenly of cardiac failure. In early puberty he was considerably upset and then became extremely well organized and adjusted until he went to college. For the first two years of college he went "haywire." He was disciplined by his parents, the authorities and his fraternity brothers. Then he became particularly well organized. He had a brilliant career but eventually suffered a sad breakdown. That case brought home to me the misfortune of premature ability to deal so effectively with one's problems that they are never really solved until one pays the price with a psychosomatic breakdown, which may lead to death.

Dr. Isador H. Coriat: My own analytic experience with these disorders has led me to a different angle of interpretation. My feeling is that these patients had at the beginning a severe character disorder or were essentially of a neurotic type. Behind the hypertension in all these patients one can, I believe, find certain specific reactions, such as hate, stubbornness, aggression or hostility. In other words, the total personality of the patient must be taken into consideration, not only the specific life situation which precipitated the hypertension or some other psychosomatic syndrome but the particular development of his personality from childhood up; then I think that one will be able to correlate a neurosis, an asthmatic disorder or a high blood pressure level with specific dynamic trends, either conscious or unconscious. In analytic work these trends are primarily unconscious, and they affect either the particular organ of which the patient complains or produce a form of hypertension.

Dr. Carl Binger: With reference to Dr. Cobb's comments, the first point at issue is one of semantics. When I said "peculiar," I meant "peculiar," not "unique." These character traits are peculiar to hypertension. They may also be peculiar to other diseases. I did not mean to imply that they were unique, nor did I intend to make a phrenologic list of neurotic character traits and say, "This is hypertension." I tried to present one life history and to show how events in the patient's childhood and subsequent events of later life led up to a certain *denouement,* which physiologically is recognized as hypertension and psychologically as a kind of decompensatory process.

Dr. Hendrick's comment seems to me much to the point. To understand so complicated a problem as hypertension, one needs to look at it both physiologically and psychologically.

Dr. Smithwick's work has been of interest to me for a long time. What the operation does in the psychologic sphere I do not know. It has proved significant to some of these patients. Certainly, many of them have shown extraordinary improvement not only in the level of the blood pressure but in their whole outlook.

In regard to Dr. Palmer's observations, I should use not the word "integration" but the word "suppression." By struggling these patients succeed in keeping down impulses which cause them a great deal of difficulty. One of the significant things about them is their incapacity for development of sustained organized neuroses. They have fleeting episodes in the form of neurotic symptoms. Perhaps, if they could sustain such symptoms, their blood vessels would be spared. This, of course, is speculation.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, April 23, 1943

Familial Periodic Paralysis. DR. ALEXANDER SILVERSTEIN.

Familial periodic paralysis is a rare disease characterized by recurrent attacks of flaccid paralysis, associated with diminution or loss of the deep reflexes and inexcitability of the muscles to electrical stimulation. Many theories have been advanced to explain these paroxysmal transient seizures. Until recently practically no treatment was known to prevent or influence the attacks.

Since 1937, when Harrington reported on the beneficial effect of potassium citrate in the treatment of this condition, interest has been greatly stimulated. Pudenz and his group, in Montreal, Canada, and Gammon and his collaborators, in Philadelphia, as well as other investigators, have published important observations on the chemical aspect of the disease. These investigators found that attacks of paralysis are associated with a pronounced fall of potassium in the serum and that the administration of an adequate amount of potassium salts brings about rapid recovery. Prompt improvement is also effected by the introduction of carbaminoylcholine chloride and mecholyl chloride into the blood stream (Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: Role of Potassium in Familial Periodic Paralysis, *J. A. M. A.* **111**:2253 [Dec. 17] 1938). Attacks have been produced by the administration of dextrose, epinephrine and ephedrine and by water diuresis.

That familial periodic paralysis seems to be an inborn error of metabolism is provocative and should stimulate work on other hereditary diseases of the neuromuscular system which at present are looked on with pessimism.

REPORT OF A CASE

A boy aged 9 years was admitted to the Philadelphia Hospital for Contagious Diseases with a condition diagnosed as acute anterior poliomyelitis. The history of the onset was that of rapidly developing ascending paralysis. When the boy was examined several hours after the onset there were complete flaccid paralysis of both lower extremities and marked weakness of the upper limbs, including the group of shoulder muscles. The deep reflexes were greatly diminished. The patient was not acutely ill; the sensorium was unaffected, and he did not complain of any soreness or pain in the muscles; there was no increased tension of the muscles of the neck or any sign of spinal involvement. The spinal fluid was not under increased pressure and showed no increase in cells. The results of all studies were within normal limits. There was no elevation of temperature or change in pulse rate. The morning after admission the patient was sitting up in bed, apparently well. Examination disclosed complete absence of all signs of paralysis. The dramatic recovery was so striking that several observers considered the diagnosis of hysteria. When the boy was questioned, it was learned that he had had a similar episode previously. I did not see the patient until three years later. A few days prior to the present admission he had a severe attack, which began early in the morning (about 4 a. m.) and persisted until the next evening. The attack consisted of complete paralysis from the toes to the neck. He was unable to open his mouth; his head "flopped" in all directions; he had great difficulty in breathing; in fact, the family thought he was dying. The patient informed me that since his discharge from the hospital he had had numerous attacks of sudden paralysis of the extremities, sometimes several a week. Invariably they occurred in the early hours of the morning, often awakening the patient from sleep. Occasionally the paralysis affected only one extremity, usually the arm. The attacks came on suddenly, without warning. Seasonal variations, especially spring and summer, gave rise to a striking increase in the frequency and severity of the attacks.

The patient is the youngest of 7 children. Five of the siblings are said to be well. The mother and her oldest child also suffered from the same attacks as the patient. The mother's paralytic attacks commenced at the age of 15 years. They occurred early in the morning and consisted of loss of power in the arms and legs, lasting about two or three hours and recurring about once every two or three months. The attacks had become much more frequent, occurring about three or four times a week and increasing in severity during the period of gestation of the youngest child (my patient). Since the age of 35 she had had no further attacks. The oldest child was stricken with infantile paralysis at the age of 18 months; this illness left him with deformity of a limb. He began to have the attacks of paralysis at 14 years of age and is said to have had about three such attacks a year. He died during a severe attack, at the age of 16. According to the mother's description, the attack began early in the morning, and within a short time he was unable to move any part

of his body from the neck down. He could hear, see, talk and swallow, and his mind was said to have been perfectly normal. Death occurred within twelve hours.

General Examination.—The boy was moderately obese, the adiposity being chiefly of the girdle type. The heart and lungs were normal. The blood pressure was 120 systolic and 70 diastolic. The disks were not choked. The pupils reacted to light and in accommodation. The significant changes were the unusual hypotonia and the alterations in the muscles, changes strongly suggesting dystrophy. The truncal and the gluteal muscles were chiefly affected. On arising from a reclining position the patient used the method of "climbing" up on his thighs so frequently seen in cases of muscular dystrophy. He was given potassium citrate, 30 grains (1.95 Gm.), three times a day for three weeks, with definite improvement in that the attacks were mild, although just as frequent. From Sept. 25, 1943 until the present time the patient has been receiving potassium chloride, 7 to 12 Gm. a day. It was found that large doses during the day would not prevent an attack the following morning. At present the patient is taking 4 Gm. at 8 a. m. and 4 p. m. and 16 Gm. at 2:30 a. m. It was noticed that during March 1943, with the frequent changes in the weather, the attacks became more frequent, and the dose had to be increased. At the beginning of an attack the patient takes 4 to 8 Gm. of potassium chloride, and improvement is noted within fifteen minutes and complete disappearance of symptoms in about two or three hours.

Comment.—I believe the clinical picture in this case is fairly typical of familial periodic paralysis, as recorded in the literature. The resemblance of periodic paralysis to anterior poliomyelitis and Landry's paralysis should be borne in mind. It should also be noted that the condition can readily be confused with hysteria, especially in sporadic cases. Periodic paralysis has been recognized as a clinical entity since 1882. The hereditary nature of the condition is evident in about 80 per cent of all cases which have been reported. The disease may be transmitted either as a dominant or as a recessive character. Sporadic cases have been described.

The condition usually makes its appearance in the first or second decade of life. The attacks have a tendency to diminish in frequency and intensity during middle life and to disappear in later adult life. The mother of my patient ceased to have attacks after the age of 35 years. Exciting factors are claimed to be strenuous exercise and intake of large amounts of carbohydrates. Most of the reported cases indicate a predilection for the male sex, the ratio of the sexes being 3:1. The disease varies in different families with respect to the mode of transmission, the time of onset, the severity and frequency of the attack and the prognosis, but the pattern of the attack seems to be more or less constant for the stricken members of the family. The attacks are more common during the night and early morning and seem to be precipitated by the patient's remaining quietly in one position for a prolonged period. Paralysis of the flaccid motor type may affect all the voluntary muscles except the face, mouth, throat and sphincter. Although death rarely occurs, in serious cases the muscles of respiration and deglutition and the muscles of the neck become involved, and death may follow. This fatal outcome occurred in the case of the patient's brother, and the patient himself had a severe attack during which he almost died. Some authors have stressed the relation of periodic paralysis to other familial diseases, such as migraine, epilepsy and hereditary myopathies. Of particular interest is the combination of periodic paralysis and dystrophy, as reported by several authors. My patient also shows signs of early dystrophy, affecting chiefly the proximal portions of the limbs and the truncal and gluteal muscle groups.

DISCUSSION

DR. J. W. MCCONNELL: I have nothing to add to this presentation except to say that it recalled to my mind a case occurring some years ago, when Dr. Spiller was holding clinics at the University of Pennsylvania. A boy was brought into the clinic paralyzed in all four extremities, with loss of all reflexes. Dr. Spiller examined him closely and said he must have acute anterior poliomyelitis. The next morning the boy was practically recovered. One of the assistants in the clinic, Dr. W. B. Cadwalader, suggested that the case might be one of familial periodic paralysis. Spiller disagreed because of the absence of other cases in the family, but Cadwalader said, "But, it has to start with somebody."

LIEUTENANT (sg) AXEL OLSEN, U. S. N. R.: Dr. McConnell says that family history must start somewhere. In 1936 I saw a man with a history of illness almost like the one just reported. His family history was perfectly clear. His muscles also were weak but appeared well developed; from his appearance one would think he should have the strength of a giant, but between his periods of acute paralysis he was as weak as a child. During the attacks of paralysis he lay completely flaccid, with electrical reactions diminishing to the vanishing point. Biopsy of muscle showed patches of disrupted fibers. The pathologist did not want to name what he saw, stating that the condition of the muscle was abnormal

but that he could not explain why. It was not the muscle of progressive muscular dystrophy. I wonder what a biopsy of this patient's muscle would show.

DR. GEORGE D. GAMMON: It might be interesting to say a word about the history of potassium therapy of this disease. In 1905 Dr. G. E. Holtzapple used potassium bromide in treatment of this condition, although at the time it was not known to him that potassium was the effective agent of relief. This remarkable practitioner of medicine, in York, Pa., discussed with his friend, Dr. William Osler, the possibility of presenting before the state medical society a family members of which suffered from periodic paralysis. Dr. Osler made the diagnosis of "family periodic paralysis" and asked Holtzapple to record the number of cases, which was the largest occurring in a single family reported in the literature.

Because migraine was associated with their condition and because migraine was attributed to vascular spasm, and the antispasmodic of the day was bromide, Holtzapple gave the members of the family potassium bromide in increasing doses until the attacks were relieved. In the editions of Osler's textbook of that period bromide is listed as a specific remedy for this condition. In subsequent editions it was dropped, because other physicians had used sodium bromide and did not obtain relief.

My first contact with this condition was made while I was studying the effect of prostigmine on myasthenia. I read a paper on that subject and Dr. W. S. McCann, of Rochester, Minn., commented that he had a patient with familial periodic paralysis who was a descendant of the family reported on by Mitchell in whom potassium citrate had aborted an attack. Mitchell recorded abortion of the paralysis, slowly, within twelve hours after administration of potassium citrate. This clue was dropped by Osler after Holtzapple had reported the effect of bromide. Earlier editions of Osler's textbook had recommended the use of potassium citrate, as proposed by Mitchell, Pemberton and Edsall. Later, Harrington stated that he was able to abort an attack with potassium citrate, but not to abolish one.

About this time I treated a man with familial periodic paralysis with large doses of potassium chloride, with immediate and dramatic improvement. With Dr. Austin and others, I then studied the serum and found a low potassium content. In England, Allen and associates had previously recorded a low potassium level in the serum and had found that potassium chloride would relieve an attack. About this time a good deal of work was reported on the relation to the disease of the potassium in the blood; these studies showed that the potassium content was lowered during a seizure and that there was no previous excessive urinary excretion of potassium during the attack.

For about four years I have treated with potassium a patient with daily attacks, and he has been able to get along fairly well by taking a dose in the early morning hours. There has been some regression of the testicles during that period, but otherwise he has been well. In this patient, inactivity undoubtedly brings on attacks. He can sit down for an hour and become weak. Characteristically, the inactivity of sleep is associated with the onset. There is a dramatic case in the literature in which a man was copying music at a desk and became paralyzed in all extremities except the one with which he was writing. Electrical stimulation of a muscle will improve its function providing the patient is not completely paralyzed at the time. Have any studies been made on the potassium content of the serum in this boy?

The potassium level can be lowered by administration of epinephrine. It appears that the weakness in these patients is due to something else. All my studies have led to the conclusion that something happens to the muscle itself, and it seemed possible that the correction of this muscular defect drew potassium out of the serum. My colleagues and I based our opinion on the abnormality of the muscle itself, in view of the fact that the electromyogram was distorted. That is an experimental observation, which may not be accepted by all investigators.

DR. A. M. ORNSTEEN: Dr. Gammon, would you draw any comparison between this disease and myasthenia gravis, the only difference being in the clinical periodicity of the paralysis?

DR. GEORGE D. GAMMON: The two diseases are almost exact opposites. Activity makes myasthenia worse and improves familial paralysis. Myasthenia is like a curarization block; the muscle itself is normal, and although potassium will help myasthenia, it will not relieve it to the degree that it does familial paralysis. The effect of prostigmine on myasthenia is comparable to the effect of potassium on familial paralysis. The studies show that myasthenia is like curarization, whereas familial paralysis appears to be a muscular defect.

Acute Ascending Paralysis; Landry's Paralysis. LIEUTENANT (sg) AXEL OLSEN, U. S. N. R.

As is well known, the group of diseases characterized by acute, rapidly ascending paralysis with minimal sensory changes has been designated by many terms. Perhaps the earliest and best known name is Landry's paralysis. It is recognized that this term is only one

applied to designate a symptom complex. The following 3 cases may not fit every neurologist's conception of Landry's syndrome, but they were felt to be sufficiently interesting to justify report, since all the patients were seen within eighteen months, all recovered and no apparent etiologic agent was discovered in the case of any of them.

REPORT OF CASES

CASE 1.—S. J. U., a white man aged 25, was admitted to the hospital on June 23, 1941, with the chief complaint of diffuse pain throughout the right leg, the pain being much worse at night. This had been preceded by three weeks of "limping with the right leg." The patient stated he did not know why he had limped, since he had had no pain in the extremity at that time. There was no complaint of numbness in either extremity. Physical examination revealed nothing abnormal except slight enlargement of the prostate and mild bilateral antritis. Neurologic examination showed slight weakness of dorsal and plantar flexion of the foot, decrease in the knee jerk and absence of the ankle jerk on the right side. Tenderness along the course of the sciatic nerve and a positive Lasegue sign were noted on the same side. The family and personal histories were not contributory except for an attack of gonorrheal urethritis three months before. The results of urinalysis, a blood count and serologic studies of the blood were normal, as was the sedimentation rate. A submucous resection was done to help eradicate the foci in the antrums, but the complaints persisted, and on July 7 the pain was extreme, being located chiefly in the right hip. The knee jerk had disappeared, and he had an obvious foot drop on the right side. The next day lumbar puncture revealed extremely xanthochromic fluid, which contained 400 mg. of protein per hundred cubic centimeters and 38 cells, of undescribed type, per cubic millimeter. By this time he complained of a twitching sensation in the muscles of his left leg. Four days later the ankle jerk was observed to be absent on the left side; the knee jerk was diminished, and weakness of the calf and the anterior tibial muscles of the left leg was obvious. The right leg was barely capable of motion. Another lumbar puncture showed a subarachnoid block; so a study with iodized poppyseed oil was carried out, revealing an obstruction at the first lumbar vertebra. Two days later (twenty days after the onset of pain) urinary retention developed. Sensory examination still gave normal results, and the white blood cells numbered 14,500. Because of the apparent block a laminectomy was done on July 16, 1941; it revealed an area of swelling in the cord, measuring 2 cm., and localized arachnoiditis at the level of the twelfth thoracic vertebra. During the week after operation the paralysis of the legs became complete, and slight hypesthesia, of diffuse type, developed in the legs, with no definite level of sensory loss. Two weeks after operation paralysis of the third nerve developed bilaterally, with dilated pupils and ptosis, and cisternal puncture revealed elevated pressure and blood-tinged fluid. The patient continued in this condition for another month; he became emaciated; a decubitus ulcer developed, and his mental attitude approached that of acute mania. On August 31, six weeks after operation, and after repeated lumbar and cisternal punctures, roentgen irradiations and vitamin therapy, it was noticed that he had a little movement in both feet, and a week later he began to void spontaneously. From then progress was steady, and he was discharged on April 2, 1942, to return to duty, with only absence of the ankle jerk and decrease in the knee jerk on the right side and very slight weakness of both flexion and extension of the right foot. He was seen again on Aug. 15, 1942, at which time his condition was unchanged.

CASE 2.—This case undoubtedly is a more typical instance of Landry's syndrome than the first case. E. F., a white man aged 50, was admitted to the hospital on April 22, 1942. His presenting complaint was prickling in the hands and feet for three days and weakness of the knees for two days. No other complaints were noted. The family history was without significance. He gave a history of a fairly severe cold, lasting one week, which disappeared a month before the present illness, and excessive alcoholism for three years, from which he recovered in 1940. He was employed in a paint-spraying establishment and worked with an unknown solvent. Physical examination showed mild arteriosclerotic changes but no other gross abnormality. Neurologic examination revealed complete areflexia, paralysis of the legs, tenderness on compression of the calves and decrease of vibration sense in the ankles. The cranial nerves were intact. The results of laboratory studies, including lumbar puncture, were normal in all respects, the spinal fluid showing 2 cells per cubic millimeter and a total protein content of 30 mg. per hundred cubic centimeters. The serologic reactions were negative, and the electroencephalograms showed no abnormality. Three days after admission the paralysis had involved his arms, and he was having difficulty in breathing. Signs of pneumonia were developing, and fluoroscopic examination of his chest revealed paralysis of the left side of the diaphragm; so treatment with sulfathiazole was started. Six days after admission no motion was present in either arm or leg, and the sensorium and cranial nerves were still intact. Two days after this he noticed a little movement in his arms, being able to

raise them three or four inches (7.5 or 10 cm.) from the bed. Five days later (two weeks after admission) urinary retention developed and catheterization was necessary. The pneumonic process was growing worse at this point, and administration of oxygen was begun. Erythematous dermatitis developed on his hands and face, becoming much more severe after five days. By that time the condition in his chest was improving, so that the sulfathiazole therapy was stopped; the dermatitis improved immediately, and his general status showed slow but steady improvement. On May 16, three and a half weeks after admission, motion was present in all joints except the ankles. He had slight hypesthesia of the lower portions of the legs, and vibration sense was absent in the ankles and wrists but was present, though decreased, elsewhere. The reflexes were still absent. Lumbar puncture on May 18 showed a protein content of 35 mg. per hundred cubic centimeters of spinal fluid. On June 11 he could walk with assistance, and on June 25 he was discharged, the reflexes being normal, the strength good and sensation normal throughout. His calves were still slightly tender, but the nerve trunks were normal on palpation.

CASE 3.—J. H. S., a white youth aged 18, was admitted to the hospital on Feb. 26, 1943. His presenting complaints were weakness of the knees, which he had first noticed three days before, while marching, and weakness of the left shoulder, which developed on the way to the hospital, in the ambulance. He had also noted a little pain in the left shoulder, some soreness of the calves and slight prickling and tingling in the toes. The family history was without significance. Two weeks before, he had had an infection of the upper respiratory tract, of three days' duration. He had noticed occasional pain in the left shoulder for the past year and acute pain in the shoulder during September 1942. Neurologic examination showed the absence of reflexes in the legs, the absence of abdominal reflexes, the presence of cremasteric reflexes and barely obtainable biceps and triceps reflexes. Sensation was normal throughout. He walked with a wide base, with the abdomen protruded, the arms swinging loosely and the knees lifted high. There were almost complete paralysis of the lower part of the left leg and pronounced weakness of the right leg. The flexors of the thigh and knee were weak, but the strength of the extensors was fair. The muscles of the abdomen were weak, as were those of the lumbar portion of the spine, but movements of the thorax and those of the diaphragm were good. There was extreme weakness of all the muscles of the right arm and of those of the left arm except the deltoid, which was paralyzed. The muscles of the neck and the cranial nerves were normal. No fibrillations were noticed, and there was no atrophy. Laboratory studies gave normal results except for a white blood cell count of 15,700. The differential count was normal, and lumbar puncture revealed normal spinal fluid. Rest in bed was the only treatment initiated; two days later his condition was definitely improved, and in a week he was up and about, only slight weakness of the left shoulder remaining. Improvement was most rapid in the legs. On March 15, seventeen days after admission, he was up and about, with no complaints. The reflexes were all present but decreased. He was discharged as well, with an entirely normal neurologic status on March 26, one month after admission. An electroencephalogram at this time revealed nothing abnormal.

Comment.—The first case may belong rather under the Guillain-Barré syndrome, though usually subarachnoid block is not a characteristic of this disease, either. It is suggested that these 3 cases represent various grades of the same disease, with the extremely acute, localized process in the first case and less severe, but more diffuse, disease in the others.

DISCUSSION

DR. A. M. ORNSTEEN: Did Dr. Olsen present these cases as instances of a particular disease of the central nervous system or merely as 3 clinical cases? Was the symptom picture classified? I am at a loss to discuss the condition; it might be Landry's paralysis.

LIEUT. ALEX OLSEN: The first case represents the Guillain-Barré syndrome very well except that there was complete block and operation showed a somewhat edematous cord with arachnoiditis. In the other cases the condition was simply an ascending paralysis; as far as I can gather, there were no peripheral neurologic signs, and the nerve trunks were not particularly tender or enlarged. I do not know what to call the condition in the first case. The sensory symptoms were minimal. The patient had a great deal of pain but no numbness.

DR. A. M. ORNSTEEN: Was there a time relation between the cases?

LIEUT. ALEX OLSEN: No, they were 3 successive cases, all representing degrees of the same disease, and I presented them because recovery was practically complete in all instances.

DR. A. M. ORNSTEEN: Did the patients have prodromal symptoms or avitaminosis?

LIEUT. ALEX OLSEN: The first patient had no prodromal signs whatever; the onset of the disease in the last 2 patients was preceded by an acute infection of the upper respiratory tract.

DR. A. M. ORNSTEEN: In general, sporadic cases of paralysis with recession of the paralysis are not unusual, and in most instances no diagnosis is made. It is well to report as many experiences of this sort as possible, so that one may classify them and decide whether one is dealing with an avitaminosis or with a disease of degenerative or virus type. I think Dr. Olsen said a subarachnoid block was typical of the condition.

DR. H. T. WYCIS: Did Dr. Olsen mention the history of work with an unknown solvent? I remember a case in which my associates and I were unable to find what the solvent was. The man had worked for Du Pont de Nemours and Company and was in constant contact with some synthetic solvent. Ascending paralysis had developed and had terminated in a complete transverse lesion of the cord. An exploratory laminectomy revealed a thickened dura with increased venous congestion about the cord, but no other abnormality. Subsequently, he made a complete recovery.

LIEUT. ALEX OLSEN: The paint solvent was mentioned because of the possible etiologic significance.

DR. J. C. YASKIN: Three conditions closely simulate Landry's paralysis: (1) acute infectious polyneuritis, with irregular distribution of the structures involved and without significant abnormalities of the spinal fluid; (2) the Guillain-Barré syndrome, and (3) acute disseminated encephalomyelitis. Acute ascending paralysis usually follows the "ascending" pattern but in rare instances may be of irregular distribution, as in 2 of Dr. Olsen's cases. The diagnosis of acute ascending paralysis, like that of early multiple sclerosis, is not always easy. Perhaps the most conspicuous objective abnormality is the disappearance of the tendon reflexes. A case in my early experience taught me much. The patient previously had had a frank psychosis, with a residence of many months at the Norristown State Hospital. On admission to the Philadelphia General Hospital he complained of weakness in all limbs and went through bizarre movements in attempting to sit or to use his limbs, and in many ways his behavior suggested hysteria. His temperature, pulse and respiration were normal, but I was unable to obtain any tendon reflexes. He died suddenly, two nights after admission to the hospital. The bizarre maneuvers were undoubtedly an attempt to substitute movements by muscles which were less affected. Another patient, who was admitted several months later and who, because of the picture previously described, was regarded by the intern and resident staff as hysterical but, on instruction, was carefully watched, suddenly manifested difficulties in breathing, from which he recovered with the aid of the respirator. The early stage of Landry's paralysis is often thought to be hysteria, but the absence of tendon reflexes should put one on guard.

LIEUT. ALEX OLSEN: In the last case I reported the physician wrote across the chart "faker."

DR. J. C. YASKIN: Later in the course of the disease the physician is again frequently fooled in regard to the prognosis. Recovery is usually not complete for many months. One patient was discharged after many months with a gloomy prognosis, only to walk in several months later in good condition. In cases with the Guillain-Barré syndrome, in the presence of considerable protein in the spinal fluid without subarachnoid block, one must be careful in making a diagnosis in order to avoid operation.

LIEUT. ALEX OLSEN: I have never seen an operation performed in the presence only of increased protein and no block, and I believe that most neurosurgeons, if they did operate, would do so merely to see what was there, and not with the hope of being able to help the patient. The acuteness of the onset, the high protein content and the lack of subarachnoid block would cause most surgeons to hesitate before making an exploration.

Cerebral and Spinal Operations in a Case of Severe Postencephalitic Tremors. DR. MICHAEL SCOTT.

A white woman aged 38 had had severe bilateral postencephalitic tremors with rigidity for twenty years. She had received intensive and persistent therapy with all members of the atropine group, including a preparation of belladonna alkaloids (rabellon), with gradual increase in violence of the tremor, which resulted in exhaustion and complete loss of use of both upper extremities. One year before this presentation (in April 1942) areas 4 and 6 of the hand and arm center in the right premotor area were ablated, with resulting complete cessation of the severe tremor on the left side during rest. The extremity was useless, however, being held in a position of flexion and contracture, with little movement of the arm and forearm and with slight return of intention tremor when movement occurred. The left leg could be moved only slightly, and a slight tremor was present at rest. Since the patient was able to walk three months after the operation, the loss of power in this extremity was attributed to the progressive rigidity of the disease and to rest in bed for one year. Four

months after the operation on the cortex, the pyramidal and the rubrospinal tract were sectioned on the right side at the third cervical level in an attempt to abolish the remaining severe tremor on the right side during rest. The operation on the spinal cord was decided on, first, because the speech center was in the left cerebral hemisphere and might be injured during the operation and, second, because it was thought that the results of the cerebral and the spinal operation in the same person, each done for tremor on the respective side, might offer valuable information on the comparative merits of the two procedures. Dr. N. W. Winkelman suggested that the rubrospinal tract be cut in addition to the pyramidal tract. It is now eight months since this operation on the spinal cord was done. The tremor during rest was abolished in the right upper extremity immediately after the operation and has not returned. The right forearm is held only slightly flexed, whereas the hand and fingers are held in the extended position, in contrast to the flexion contracture of the left hand and fingers. The forearm and the wrist can be flexed and extended, and similar movements can be executed to a moderate degree by the fingers. The patient can carry to her lips a small glass of water placed in her right hand without any tremor. When the hand is returned slowly to the bed, a slow, transient tremor appears and stops in a few minutes. This tremor seems to occur only when the forearm is extended. No skilled movements are possible with the right hand, the hand being held in the position of a "salute," with the movements like those of a puppet. The right lower extremity could be moved slightly after operation but is now in flexion, with extreme rigidity. The loss of power in this extremity was augmented by the deep pyramidal section. The patient's medication, which consisted of scopolamine hydrobromide, $\frac{1}{75}$ grain (0.8 mg.) every four hours when she was awake, has not been changed during the year in order that the surgical procedures might properly be evaluated.

Conclusions.—No definite conclusion can be drawn from this case as to the relative merits of the cortical and the spinal operation. Since the amount of cortical tissue removed depends on the delineation of the area by electrical stimulation, different operators will remove greater or lesser areas, with different results. The same variability applies to the depth of the spinal incision; yet this could be more accurately controlled than the extirpation.

The results to date show that either operation will abolish the tremor at rest, and they tend to confirm Putnam's opinion that pyramidal tractotomy, if confined to the fibers of the upper extremity, may offer better results than the cortical operation.

Either operation should be reserved only for patients with a tremor of such severity as to make the extremity useless. One cannot promise the patient that the hand will not be useless after the operation, although the tremor may be abolished.

Comparative observations were made after both operations with respect to tremor at rest and intention tremor, return of motor power, various reflexes, sensation and posture and final use of the extremities.

The posture of the hands and fingers following spinal section of the pyramidal and rubrospinal (?) tracts is striking, and in notable contrast to that following ablation of areas 4 and 6.

A Hoffmann sign was not obtained on the side of the pyramidal section.

Moving pictures, illustrating the patient's condition after each operation, were presented.

DISCUSSION

DR. GEORGE D. GAMMON: My associates and I recently had a patient with extreme parkinsonian rigidity and pain in the right leg on whom Putnam's operation was performed. Flaccid paralysis of the right side was maintained for five weeks; motor function is now beginning to return. The operation abolished his tremor, but he will not obtain enough voluntary power to be at all useful in either the arm or the leg.

Book Reviews

An Introduction to Group Therapy. By S. R. Slavson. Price $2. Pp. 352. New York: The Commonwealth Fund, 1943.

The author of this book is supervisor of group therapy at the Jewish Board of Guardians, a social agency in New York city which is equipped to handle psychiatric problems arising in their clientele, both individually and in groups. Although the title of the book suggests that the author might discuss group therapies in general, it is only in a short chapter near the end of the book that he briefly presents various types of group therapy. Throughout the book references are made to psychologic factors common to all forms of group therapy. The book is in the main, however, devoted to describing activity group therapy as practiced at the Jewish Board of Guardians.

The groups are usually limited to 6 or 8 persons, and at present they are made up of children whose ages fall within a 2 year span and who are less than 13 or 14 years old. The material is essentially limited to rather superficial problems of rejected children who have had some difficulty in making a social adjustment to groups in the community, whether family, school or other children. They are usually children who are somewhat over-aggressive or submissive and withdrawn, or who have bad habit formations. Psychopathic personalities and children who are extremely narcissistic, excessively sadistic or masochistic or overtly homosexual are excluded. Children who have been found inaccessible for individual psychotherapy by virtue of being rather uncommunicative are also referred for exclusive group therapy. At times the group form of treatment is used to supplement individual psychotherapy—for instance, when there is parental opposition to the latter form of treatment. Some families seem to accept the idea of the child's joining a "club" more readily than that of having him come for psychiatric treatment.

The activities of the group are varied. In the main the children are occupied with constructing whatever they desire, the material and means for doing so being made available to them. At each session refreshments are served, an occasion offering an opportunity for observation of the child in another social experience. Other activities, such as visits to museums or theaters and outings, are decided on by members of the group.

There are frequent aggressive outbursts, sometimes directed against other members of the group or against the work material. These outbursts are not interfered with by the group therapeutist, who will try to limit them only in extreme situations. The child who enters the group is accepted with all his faults and given "unconditional love." He is exposed to a permissive environment in which the expression of free activity is limited only by the other members of the group, with a minimum of interference by the group therapeutist.

A chapter is devoted to the qualifications of the group therapeutist and to the role that he should play. He is considered by the author as a catalyst, although by virtue of his age and position he does represent authority to the children. Except, however, in extreme cases, he should not use this authority, nor is he supposed to show preference to any individual members of the group or to become involved in their individual quarrels. If at times it becomes necessary to limit certain activities, the therapeutist uses the "office" as the representative of authority. On occasions, in an attempt at ego inflation in the case of a particularly beaten-down child, the therapeutist may resort to praise when this would ordinarily not be called for. Interpretations of the children's behavior are not made. In his discussion of the qualifications of the group therapeutist, the author suggests that occupational therapeutists could probably best be molded into suitable personnel.

As a result of the treatment, the child's problem-producing propensities are said to increase. The author feels that many such children have not been accepted by a group because of their own hostility toward the group. A lessening of this hostility minimizes the hostility of the environment toward him, and he therefore becomes more acceptable to the group. The development of feelings of self acceptance in the child also makes him able to accept other people. The author claims that treatment seeks to reduce anxiety arising from destructive impulses and from the fear of punishment or rejection. In general, also, the treatment aims to increase the child's tolerance to frustration. One of the potent factors in facilitating the success of group treatment is the existence in the child of "social hunger," the desire to be a part of the group and to be accepted by the group (Trotter's herd instinct [?]). As the result of this therapeutic process, there develops a group superego, which is more tolerant

and of a socializing nature. The outcome of the total experience of group therapy is a change in the ego structure of the child.

Throughout the book there are numerous case illustrations, and one chapter is devoted to a detailed discussion of 5 cases, with reproduction of actual scenes during group therapy. Although there are no statistics on the achievement of treatment, the author gives the impression that the results are rather good. It appears to the reviewer that for a limited group of patients this form of treatment might be useful. After reading the book, one has an excellent idea of the methodology of activity group therapy as practiced by the Jewish Board of Guardians.

Rehabilitation of the War Injured: A Symposium. Edited by William Brown Doherty, M.D., and Dagobert D. Runes, Ph.D. Price $10. Pp. 684. New York: Philosophical Library, Inc., 1943.

This book is a collection of articles reprinted from medical journals on every phase of rehabilitation of the war injured. These papers are arranged under the headings: "Neurology and Psychiatry"; "Reconstructive and Plastic Surgery"; "Orthopedics"; "Physiotherapy"; "Occupational Therapy and Vocational Guidance"; "Legal Aspects of Rehabilitation," and "Miscellaneous." The articles apparently are all by recognized experts in the specific fields. They are all concerned with questions of particular interest at the moment. It is of special value to physicians of the United States that so many of the papers are by leading physicians in England and present the results of experience there during the years before we in America entered the war.

The articles which bear directly on neurology and psychiatry are well chosen and are notable for the detailed information on each subject. The chapters on sequelae of war head injuries, by D. Denny-Brown, and on the rehabilitation of war head injuries, by W. McKissock and by Brigadier Hugh Cairns, offer statistics and material as yet unavailable from the wounded of our armed forces.

There is an article on treatment of speech disorders, by Stanley Cobb; one on rehabilitation after injuries to the central nervous system, by Geoffrey Jefferson, and one on the psychologic reactions to injury, dealing largely with the phantom limb concept, all of which are specifically detailed for use at the present moment.

In the sections on orthopedics and physical therapy there are several practical articles on the treatment of nerve injuries. One on the use and abuse of splints in treatment of nerve injuries, by T. P. McMurray, and one on massage and exercise in the treatment of nerve suture and repair, by James Mennell, are particularly good because of their use of sound physiologic principles, together with practical knowledge acquired from long experience. There is much that is new and interesting in the section on occupational therapy and vocational guidance. Again, the experience of the English in social rehabilitation of the war injured is of considerable value to this country at present.

The last two articles, by Lieutenant Commander James C. White, deal with the effects on the limbs of the injury, immersion and systemic changes coincidental with prolonged exposure. New syndromes are described here, and their underlying anatomic and physiologic processes are outlined. There are many details as to the effects of various treatments.

In general the book is excellent. It presents in a relatively small space the reports of experts on many aspects of rehabilitation. The detail is such that those seeking practical information may obtain it, and the scope of articles is sufficiently wide that they may be of interest to the civilian neuropsychiatrist at any time, as well as to the medical officer in the present emergency. The bibliography is useful and usable. There are few symposiums which so effectively accomplish their aim. The editors are to be complimented particularly on their choice of authors, which necessitated a wide knowledge of the field, and one not usually found in a time of emergency such as the present.

The faults of this book are minor. It is poorly proofread, and the photographs are scarcely worth their space. It would have been relatively simple to have given more detail to the position and capacities of the authors, some of whom are mentioned only by name, without title, and this would have added both interest and weight to what they have written.

Physiological Psychology. By Clifford T. Morgan. Price, $4. Pp. xii plus 623, with 176 illustrations. New York: McGraw-Hill Book Company, Inc., 1943.

Morgan devotes about two thirds of his excellent book to the background of psychology, to the anatomy and physiology that make psychology possible. Much of this material is already in the books on neurophysiology, but the point of view and the control that the author exerts over his material are valuable and interesting, as well as soundly developed. The author enjoys a peculiar position, indeed, being able to draw on the findings not only

of the medically inclined physiologists but of workers in more academic realms. In any event, the conclusions are emphasized by numerous charts and curves that reveal the basic mechanisms involved.

The book follows the conventional pattern in presenting material concerning the development and differentiation of the nervous system and its functions, with special chapters on the various senses, marking considerable recent advances in scientifically controlled experiments. Chapters on emotion, sleep and activity, instinctive behavior, mating behavior and bodily needs serve to facilitate the transition to an excellent "Survey of Adaptive Behavior," which is the author's most distinctive and personal contribution. Here he is able to collect, integrate and expand the ideas of numerous predecessors, beginning with Claude Bernard, on the humoral motive factor and the central motive state that underlie a large proportion of the strivings and total behavior of the living human organism.

"The *set* aspect of motivation, *i. e.*, the potentiality of perceiving various aspects of the external situation and reacting to them in an organized way, is dependent chiefly upon the cerebral cortex. Without the cortex, the motive state eventuates only in the immediate general and specific forms of behavior associated with the c.m.s., or humoral motivating influence giving rise to it; the more complex perceptions and organized responses which issue from the priming property of the c.m.s. are lacking." This summary introduces a survey of learning that reaches into the field of psychology itself, including symbolic processes.

The author admits that he has tried to get away from the armchair type of psychology, or the subjective method of approach, and consequently has relied mostly on animal experimentation, pointing out again and again special experiments that should be performed in order to test the theories developed. In some ways, therefore, the book lacks the charm of personal experiences and their physiologic correlates. If there is one field in experimental psychology that has been slighted in the book, it is that of experimental neuroses, which receives only two pages. A bibliography of 830 references, together with an excellent index, renders this work particularly valuable for the advanced student.

The Nature and Treatment of Mental Disorders. By Dom Thomas Verner Moore, O.S.B., Ph.D., M.D., with a foreword by Edward A. Strecker, M.D. Price, $4. Pp. viii, plus 312. New York: Grune and Stratton, Inc., 1943.

Father Moore, from his long experience as both priest and physician to the mind, makes in this book a "sincere attempt to make use of whatever is available in psychology or physiology to clarify the concept of mental disorder or ameliorate any abnormal condition of the human mind." "Successful psychiatry," he continues, "can neglect neither the psychic nor the somatic." While he does not specifically emphasize the power of God, this factor is the constant K that enters into almost every equation of human personalities that so richly illustrates this small, readable volume.

The book starts off with a brief and succinct summary of the various concepts of psychopathology held by Freud, Jung, Adler and Alexander, with critical comments concerning their lack of control observations. "It is high time for psychoanalytic writers to test their theories of the origin of mental disorder by empirical study and statistical procedures." Dr. Moore's own tetrachoric correlations leave something to be desired in the way of precision in definition of symptomatology, although in his previous works, to which he refers repeatedly, the characteristics investigated are evidently more thoroughly analyzed. It suffices in the present volume for the author to find a certain correlation between "stereotypism of attitudes," "giggling" and "loss of finer sensibilities" picturing in the syndrome of schizophrenia. By means of these intercorrelations, the author presents an apparently novel syndrome, paranoia irritabilis.

The book is somewhat of the "closed compartment" type, with discussions of these statistical studies and the erection of syndromes, contrasted with references to the physiologic foundations of emotional expression and hypothalamic activity, on which is engrafted a psychotherapy as eclectic as the best, with the beneficence of God as an explanation for some of the otherwise inexplicable successes recounted. It must be accepted as a personal, almost autobiographic, account of adventures in psychopathology and psychiatry by a man who has experienced two fundamentally different disciplines and who attempts, with mottlings of success and failure, to bring the two into greater harmony. Since this volume cannot be considered a textbook of psychiatry of any pretensions, it is incongruous to find some 30 pages devoted to standard nomenclatures of disease as applicable to psychiatry.